Identifying and treating cognitive impairment in fibromyalgia and chronic widespread pain: an epidemiological study and a feasibility study

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Thesis submitted in partial fulfilment for the degree of Doctor of Philosophy

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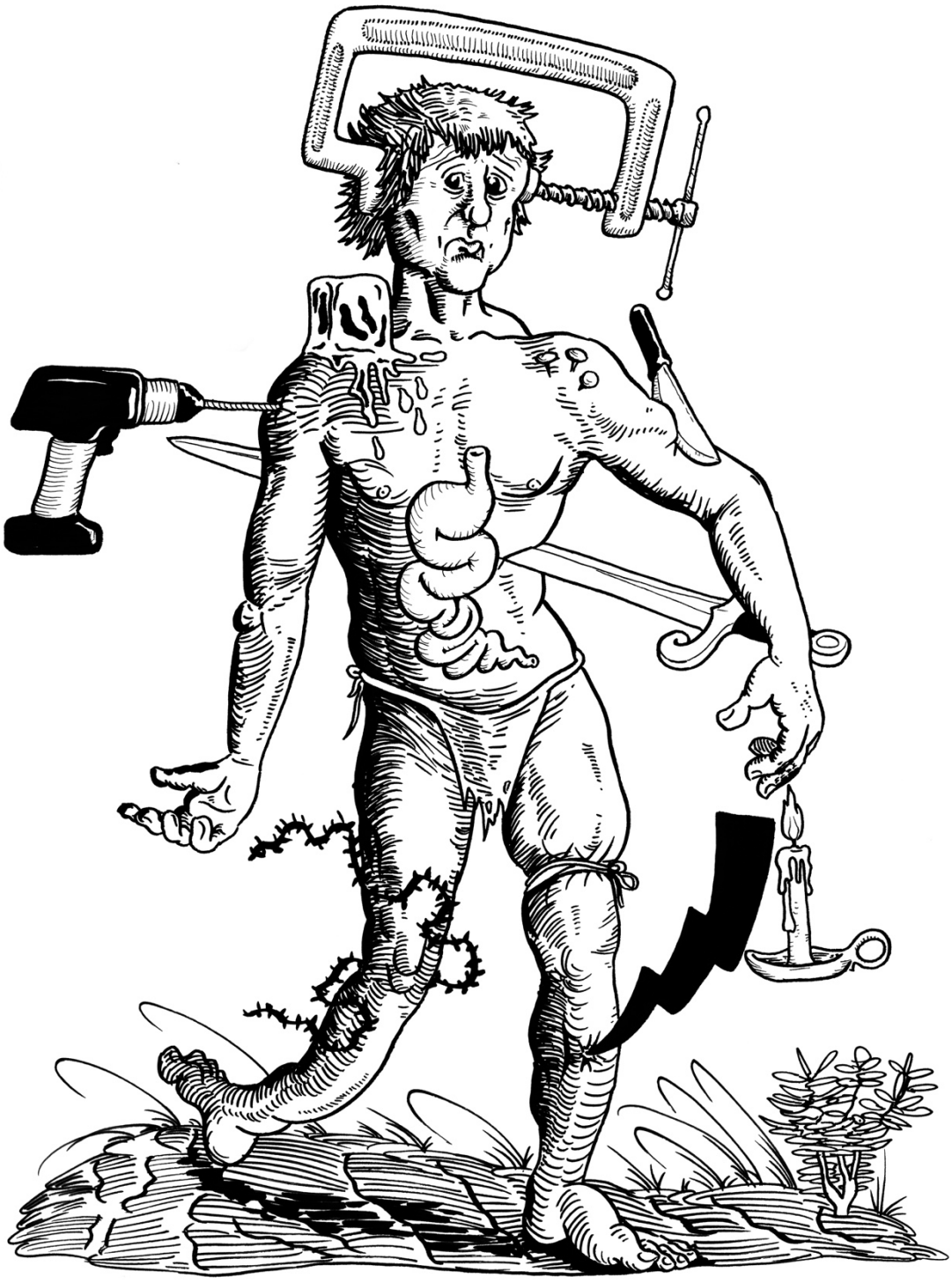

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Abstract

Fibromyalgia is a chronic pain condition characterised by widespread pain in the presence of symptoms including sleep disturbance and cognitive difficulties, also known as "fibrofog". It is the prototypical example of nociplastic pain, which arises from dysfunctional pain processing in the central nervous system, notably in the descending pain modulation system (DPMS). Nociplastic pain exists on a spectrum, with varying degrees of pain widespreadness and other symptoms such as sleep disturbance. Although cognitive difficulties are common in these disorders, the long-term cognitive consequences are uncertain, as is the role of sleep. Cognitive symptoms in insomnia can be successfully treated with cognitive behavioural therapy for insomnia (CBT-I), which thus represents a promising therapeutic approach for alleviating cognitive difficulties in fibromyalgia.

The aim of this thesis was to investigate the relationship between fibromyalgia, nociplastic pain, and cognitive impairment, with a particular focus on sleep disturbances. This was achieved through two key studies: an epidemiological study of nociplastic pain and cognition in UK Biobank, a large population-based cohort study of middle-age British adults; and an observational study evaluating sustained attention in patients with fibromyalgia, with an embedded feasibility trial of digital CBT-I (*PainLESS*).

In UK Biobank, nociplastic pain severity was shown to have a cross-sectional association with worse executive function but was not associated with faster decline in cognitive abilities. This cross-sectional relationship was mediated by pain intensity and sleep disturbance. In the same cohort, I also showed that nociplastic pain was associated with altered functional and structural connectivity within the DPMS, which in turn mediated the relationship with executive function.

In a cohort of patients with fibromyalgia, symptom severity was associated with impaired sustained attention, which in turn was also mediated by sleep disturbance and altered connectivity within the DPMS on neuroimaging.

Finally, a trial of digital CBT-I nested within this cohort was feasible in fibromyalgia.

The work in this thesis therefore demonstrates that sleep disturbance contributes to cognitive impairment in fibromyalgia, representing a promising therapeutic target. A trial of digital CBT-I in fibromyalgia may improve cognitive outcomes in future patients with the disorder.

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Ní neart go cur le chéile. This DPhil would not have been possible without the encouragement and time of countless others.

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Abbreviations

ANOVA	Analysis of Variance
BC-CCI	British Columbia Cognitive Complaints Inventory
BOLD	Blood-Oxygen Level Dependent
CBT	Cognitive Behavioural Therapy
CBT-I	Cognitive Behavioural Therapy for Insomnia
CBT-P	Cognitive Behavioural Therapy for Pain
CCA	Canonical Correlation Analysis
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
CNS	Central Nervous System
CPM	Connectome Predictive Modelling
D'	Sensitivity
dCBT-I	Digital Cognitive Behavioural Therapy for Insomnia
dlPFC	dorsolateral Prefrontal Cortex
dMRI	diffusion-weighted magnetic resonance imaging
DN4	Doleur Neuropathique 4
DPMS	Descending Pain Modulatory System
EF	Executive Function
FIQR	Fibromyalgia Impact Questionnaire Revised
FM	Fibromyalgia
FMI	Fibromyalgia Index
fMRI	functional Magnetic Resonance Imaging
FSS	Fatigue Severity Scale
GAD-7	Generalised Anxiety Disorder 7-item
GAM	Generalised Additive Models
ISI	Insomnia Severity Index
JSS	Jenkins Sleep Scale
LMM	Linear Mixed-effects Model
MOS-SS	Medical Outcomes Study Sleep Scale
NRS	Numerical rating scale
NVT	Number Vigilance Task
PAG	Periaqueductal grey
PainLESS	*Characterisation of **Pain** in Patients with Musculoskeletal Disease: A **L**ongitudinal, Observational Study with an **E**mbedded Feasibility Window of Opportunity **S**leep **S**tudy*
PHQ-9	Patient Health Questionnaire 9-item
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
rACC	Rostral Anterior Cingulate Cortex
RCT	Randomised Controlled Trial
RMSEA	Root Mean Square Error of Approximation
ROI	Region of Interest
RSFC	Resting state functional connectivity
RT	Reaction time
RTV	Reaction time variability
RVM	Rostral Ventromedial Medulla
sgACC	subgenual Anterior Cingulate Cortex
SPACE	Sleep, Pain, Affect, Cognition, Energy
SSS	Symptom Severity Score
TCA	Tricyclic antidepressants
TLI	Tucker Lewis Index
TST	Total sleep time
VAS	Visual Analogue Score
WPI	Widespread Pain Index

Selected publications and presentations arising from this work

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- *Manuscript described in Chapter 2, Joint first author*

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- *Informs content of Chapter 1: General Introduction. I created the figures which were later rendered by the in-house team at Nature Reviews Neurology.*

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Wall A*, **Kelleher E***, Majithia V, Irani A. Understanding pain in psoriatic disease. **IFPA-WPPAC 2024**, 2024.

- *Joint first author*

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Brain Signatures of Nociplastic Pain: Fibromyalgia Index Linked to altered descending pain modulation in Population-Based Neuroimaging Study.
Eoin Kelleher MB BCh, Frederik Lange DPhil, Vishvarani Wanigasekera DPhil, Trishna Rathod-Mistry PhD, Thomas Nichols PhD, Ben Seymour PhD, Irene Tracey DPhil, Andrew Reilly Segerdahl DPhil, Anushka Irani DPhil

- *Manuscript based on content in Chapter 4*

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Kelleher E, Wall A, Sanchez-Santos M, Wanigasekera V, Irani A. Centralised pain in early rheumatoid arthritis predicts worse bodily pain outcomes. Rheumatology, April 2024; Vol. 63, ppS144

Multi-site chronic pain and cognitive performance: a cross-sectional study of UK Biobank Authors: **Kelleher EM**, Tai XY, Rathod-Mistry T, Nichols T, Tracey I, Irani A. British Pain Society Annual Scientific Meeting, Glasgow. May 2023

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1 Chapter One: General introduction

1.1 Chronic pain and cognition

Chronic pain represents a substantial global health burden, affecting up to half the population and significantly contributing to disability and reduced quality of life[365]. Traditionally viewed as a symptom secondary to other conditions, the classification of chronic primary pain as a standalone diagnosis in the most recent International Classification of Diseases (ICD)-11 marks a paradigm shift in its conceptualisation[229; 418]. Exemplified by fibromyalgia, chronic primary pain is thought to be predominantly driven by nociplastic mechanisms, characterised by widespread pain and sensory hypersensitivity resulting from dysfunctional central nervous system (CNS) pathways[159]. Beyond pain, these conditions feature clusters of symptoms—including the SPACE symptoms (sleep, pain, affect, cognition, and energy)—reflecting potential shared CNS dysfunction[402]. Among these, cognitive symptoms such as difficulties with concentration and memory (commonly referred to as “brain-fog” or “fibrofog”) are pervasive, significantly impacting patient outcomes and quality of life[247; 326]. Addressing these cognitive symptoms has been identified as a key research priority by the James Lind Alliance[158].

This DPhil seeks to advance our understanding of objective cognitive impairments in fibromyalgia and nociplastic pain, focusing on its epidemiology, its relationship with co-morbid symptoms like sleep disturbance, and its progression over time. By leveraging large-scale neuroimaging data, this work aims to elucidate functional and structural

brain changes associated with these conditions, potentially uncovering mechanisms that could inform treatment strategies. If specific neuroimaging correlates of cognitive symptoms are identified, they could also serve as objective biomarkers, addressing a significant gap in the field. Furthermore, investigating the feasibility of digital interventions such as *Sleepio*—an established and validated digital cognitive behavioural therapy for insomnia (CBT-I) platform—may pave the way for scalable treatments to alleviate these cognitive symptoms.

By improving our understanding of cognition in nociplastic pain and developing tailored interventions, this project has the potential to improve quality of life, enable better engagement with other therapeutic modalities, and reduce healthcare utilisation and costs. Ultimately, this work aims to address an important unmet need for effective treatments in patients with nociplastic pain conditions such as fibromyalgia.

1.2 **Understanding Fibromyalgia and Nociplastic Pain**

1.2.1 **Definitions and mechanisms**

Pain, as defined by the International Association for the Study of Pain (IASP), is “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage”[365]. Chronic pain, which persists or recurs for longer than three months, is increasingly recognised as a distinct disease entity with unique biological mechanisms, consequences, and treatment requirements[451; 454; 455]. The IASP categorises chronic pain into three principal mechanisms: nociceptive pain, arising from actual or threatened tissue damage; neuropathic pain, resulting from a lesion or disease of the somatosensory nervous

system; and nociplastic pain, which arises from altered nociception without evidence of peripheral nociceptor activation or somatosensory system damage[365]. Nociplastic pain represents the newest mechanistic framework[286].

1.2.2 Clinical presentation and diagnostic challenges

Fibromyalgia and related nociplastic pain syndromes are characterised by a spectrum of multidimensional symptoms, including widespread pain, cognitive impairments, sleep disturbance, fatigue, and sensory hypersensitivity[230] (**Figure 1-1**). These conditions often defy conventional diagnostic criteria, making their prevalence challenging to estimate precisely. However, data suggest that chronic primary pain conditions such as fibromyalgia, irritable bowel syndrome, and chronic low back pain are highly prevalent, affecting approximately 2–6% of the population for fibromyalgia and 8–11% for chronic widespread pain[14; 159].

While typical presentations, such as those in fibromyalgia, often involve widespread and poorly localised pain, individual characteristics vary in terms of location, severity, and descriptors, as well as the dominant clinical syndrome. Therefore, it is more helpful to consider nociplastic pain as a spectrum of different pain features rather than a single, specific presentation[159].

Severity of nociplastic pain can be measured using the Fibromyalgia Index (FMI), derived from the 2016 Revised American College of Rheumatology (ACR) Fibromyalgia Survey Criteria[159; 499]. The FMI, when used as a continuous measure of nociplastic severity, predicts surgery and opioid non-responsiveness following arthroplasty[65] and hysterectomy[217].

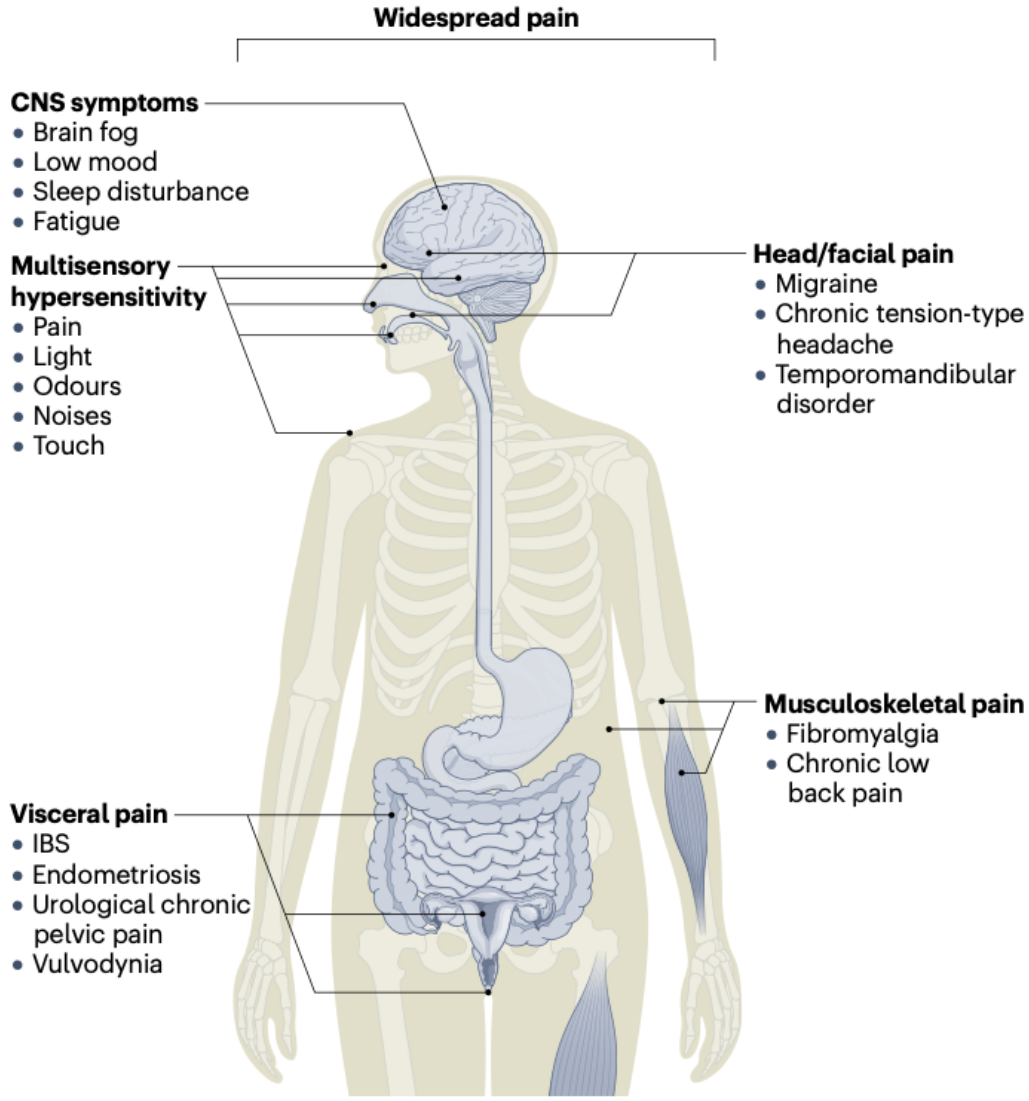


Figure 1-1. Central nervous system-mediated features of nociplastic pain.

In addition to widespread pain that can involve the viscera, head and face, and musculoskeletal system, people with nociplastic pain often experience a cluster of central nervous system (CNS)-mediated symptoms, including cognitive disturbances, mood problems such as depression and anxiety, unrefreshing sleep, fatigue, and multisensory hypersensitivity. Individuals with nociplastic pain are commonly diagnosed with multiple chronic primary pain conditions (also known as chronic overlapping pain conditions). IBS, irritable bowel syndrome. Reproduced with permission from Kaplan, Kelleher, et al. 2024[230]

1.2.3 Risk factors for nociplastic pain

Nociplastic pain syndromes, including fibromyalgia, arise from a complex interplay of socio-demographic, biological, psychological, and lifestyle factors. While nociplastic pain was only defined in 2016, insights from chronic primary conditions such as

fibromyalgia highlight common risk factors that shape vulnerability to these conditions. Understanding these influences provides a foundation for identifying covariates in this thesis and justifying the focus on modifiable pathways such as sleep disturbance.

1.2.3.1 Socio-demographic risk factors

Female sex is a well-documented risk factor, with conditions such as fibromyalgia affecting women approximately 1.5–2 times more frequently than men, especially post-puberty[307; 312]. Hormonal influences, such as fluctuations in oestrogen, and gender-specific life stressors, including adverse childhood experiences, may play a role[106; 186; 472].

Age exhibits a nonlinear relationship with chronic pain. Conditions like fibromyalgia peak in midlife or later, complicating their differentiation from degenerative pain conditions associated with aging where cumulative nociceptive input can lead to central sensitisation[506].

Additionally, **socioeconomic deprivation** and **lower educational attainment** are associated with nociplastic pain, potentially reflecting the cumulative burden of environmental, occupational, and psychosocial stressors[284]. However, this relationship may be bidirectional; pain itself can also negatively impact educational attainment and employment, perpetuating cycles of disadvantage[336].

1.2.3.2 Genetic risk factors

Nociplastic pain conditions, such as fibromyalgia, are complex disorders that display heritability similar to other common chronic illnesses[125]. Genome-wide association studies implicate **genes** involved in serotonergic, adrenergic, and immune pathways, suggesting interactions between genetic susceptibility and environmental triggers[223].

Epigenetic modifications, influenced by early life stressors, may further amplify risk by modulating CNS function[113].

1.2.3.3 Psychological risk factors

Psychological factors, including **depression**, **anxiety**, and **catastrophising** beliefs, are intertwined with nociplastic pain[306]. While these conditions can predispose individuals to heightened pain perception via maladaptive thought processes and altered pain-related brain activity[45], they are also frequently consequences of chronic pain itself. For many patients, improvements in pain lead to marked reductions in psychological distress[194; 258; 401]. In children, predictors of nociplastic pain include somatic symptoms and sleep disturbances, rather than anxiety or depression, emphasising the importance of sleep as a central factor[231].

1.2.3.4 Lifestyle and behavioural risk factors

Obesity is associated with increased nociceptive input from altered joint biomechanics and a systemic pro-inflammatory state, both of which can drive central sensitisation[117; 350; 485].

Regular **physical activity** enhances descending pain inhibition, while sedentary behaviour reduces pain inhibition and increases vulnerability to central sensitisation[335; 415]. Conversely, cessation of physical activity can precipitate nociplastic symptoms, such as widespread pain and fatigue[175].

1.2.3.5 Sleep disturbances

Sleep disturbances are an important risk factor for nociplastic pain, with evidence from experimental and epidemiological studies[88].

In the 1970s and 1980s, Harvey Moldofsky carried out a series of seminal experiments that significantly advanced our understanding of the mechanistic link between sleep disturbance and fibromyalgia. His work was among the first to demonstrate that specific alterations in sleep physiology can directly induce the cardinal symptoms of fibromyalgia, including widespread musculoskeletal pain, fatigue, and mood disturbance.

In his 1975 study, Moldofsky explored the association between electroencephalographic (EEG) sleep characteristics and symptomatology in ten patients diagnosed with ‘fibrositis’, a term contemporaneous with what is now recognised as fibromyalgia, although it should be noted that diagnostic criteria have evolved in the 50 years since[324]. He observed that 7 out of 10 patients exhibited a distinctive EEG pattern during sleep in which relatively fast alpha wave activity (7–11 Hz) intruded into deep non-rapid eye movement (NREM) sleep, typically characterised by slow delta waves (<4 Hz). This finding, which he termed “alpha-delta sleep,” was associated with increased next-morning pain, stiffness, and poor self-reported sleep quality. Importantly, alpha-delta sleep was not observed in healthy controls with normal sleep or individuals with somatoform pain disorders, suggesting a specific pathophysiological link to fibromyalgia. Moldofsky posited that this pattern reflected a state of hyperarousal or internal vigilance during sleep, which prevented entry into restorative slow-wave sleep and could explain the non-refreshing sleep frequently reported by fibromyalgia patients.

In a parallel arm of the same study[324], Moldofsky evaluated the effects of selectively disrupting deep sleep in healthy adults. Six male volunteers underwent two nights of undisturbed sleep, followed by three nights of selective Stage 4 NREM sleep disruption via auditory stimuli triggered by the appearance of delta waves. These arousals, which aimed to mimic the micro-arousals observed in fibromyalgia, were subtle enough that they did not affect total sleep time and were largely not recalled by participants. Nevertheless, they significantly reduced time spent in Stage 4 sleep. By the end of the deprivation period, participants developed transient symptoms strikingly similar to fibromyalgia, including diffuse musculoskeletal pain, increased pressure-point tenderness, fatigue, and mood disturbance. These symptoms resolved following two nights of recovery sleep during which deep NREM sleep was restored. This study was among the first to demonstrate a causal relationship between specific sleep architecture disruption and fibromyalgia-like symptoms.

Building upon these findings, Moldofsky conducted a follow-up experiment in 1976 comparing the effects of selective disruption of Stage 4 NREM sleep versus rapid eye movement (REM) sleep[323]. Seven participants were subjected to REM sleep disruption, while six underwent Stage 4 NREM sleep disruption. Of note, only disruption of deep NREM sleep induced symptoms characteristic of fibromyalgia. REM sleep disruption, while associated with increased awakenings and dream recall, did not induce widespread pain or fatigue. This highlighted the specific importance of deep, or slow-wave, sleep (SWS) in fibromyalgia symptomatology.

In a 1980 study, Moldofsky further examined the dose-response relationship between sleep architecture and symptom severity in fibromyalgia[321]. Fifteen fibromyalgia patients were randomised to receive either L-tryptophan (5g) or chlorpromazine (100mg) nightly in a sleep laboratory setting. Using PSG, Moldofsky found that chlorpromazine was associated with increased NREM Stage 4 sleep and reduced next-morning pain, while L-tryptophan did not significantly alter sleep architecture or symptoms. Importantly, across both groups, an increased proportion of alpha wave activity during NREM sleep was associated with greater next-day muscle tenderness, while a higher proportion of delta activity was associated with reduced pain and anxiety. This established a dose-response relationship between alpha-delta sleep intrusion and fibromyalgia symptom severity, reinforcing the role of this sleep characteristic as a mechanistic contributor to pain and fatigue.

Further evidence supporting the involvement of sleep in fibromyalgia pathogenesis came from Moldofsky's observation that similar alpha-delta sleep patterns could be induced in healthy individuals following febrile illness[318]. This suggested that immune activation, such as that occurring during infection, might serve as an initial trigger for sleep disruption, and subsequently, fibromyalgia symptom development. Supporting this, his 1986 work showed that interleukin-1 (IL-1), a key sleep-regulating cytokine, increased during the onset of SWS in healthy adults[322]. These findings imply that chronic immune dysregulation could disturb sleep, potentially contributing to development of fibromyalgia in susceptible individuals.

In 1997, Moldofsky and colleagues demonstrated that fibromyalgia patients performed more poorly than controls on complex cognitive tasks, an effect hypothesised to result from a greater proportion of time spent in light (Stage 1) NREM sleep[227]. This offers a potential mechanism for the “fibrofog” commonly reported by patients and supports the broader role of disordered sleep in cognitive dysfunction associated with fibromyalgia.

Finally, in a 2001 study, Moldofsky and Roizenblatt used high-resolution PSG to examine patterns of alpha activity during NREM sleep in 40 female fibromyalgia patients and 43 healthy controls[374]. They identified three distinct alpha wave phenotypes: phasic alpha (intermittent bursts), tonic alpha (continuous activity), and low alpha activity. Notably, phasic alpha, corresponding to the “alpha-delta” pattern observed in earlier studies, was present in 50% of fibromyalgia patients and most strongly associated with post-sleep pain and subjective reports of non-refreshing sleep. These findings provide further evidence that alpha intrusion may represent a biomarker for the disrupted sleep architecture in fibromyalgia.

Moldofsky’s findings have been replicated by several subsequent studies. Older et al. reported that noise-induced disruption of SWS in healthy adults induced generalised pain and fatigue[341]. Similarly, Lentz et al. found that three consecutive nights of SWS disruption in middle-aged women led to increased muscle tenderness, pain, and fatigue[264]. Although alpha activity was not consistently observed in these studies, methodological differences may account for this, particularly the extent to which Stage 2 and 3 sleep were also disrupted.

The presence of alpha intrusion during sleep has been corroborated in multiple EEG studies of fibromyalgia patients. While alpha wave activity is not unique to fibromyalgia, the phasic “alpha-delta” sleep pattern appears to be particularly characteristic of patients with non-refreshing sleep and post-sleep pain. This pattern may reflect a state of heightened nocturnal arousal that fragments deep sleep and prevents adequate restoration.

Thus, non-refreshing sleep in fibromyalgia may be explained by the intrusion of alpha waves into slow-wave sleep, representing an overly vigilant sleep state. Evidence for this includes the reproducibility of fibromyalgia symptoms through selective deep sleep disruption, the dose-response relationship between alpha activity and symptom severity, and the association between poor sleep quality and post-sleep pain. Epidemiological studies confirm that self-reported sleep problems are strongly predictive of widespread pain and nociplastic syndromes[88]. These studies collectively support the notion that fibromyalgia may be, at least in part, a disorder of sleep architecture and that interventions targeting sleep physiology could play a key role in managing its symptoms.

1.2.4 Brain networks in pain processing

Pain arises from the coordinated activity of complex brain networks influenced by nociceptive input, context, emotion, and cognition. In nociplastic pain conditions, such as fibromyalgia, CNS processes can amplify or sustain pain in the absence of ongoing

tissue or nerve damage. This section focuses on key brain network changes relevant to the thesis, with a focus on the descending pain modulation system (DPMS).

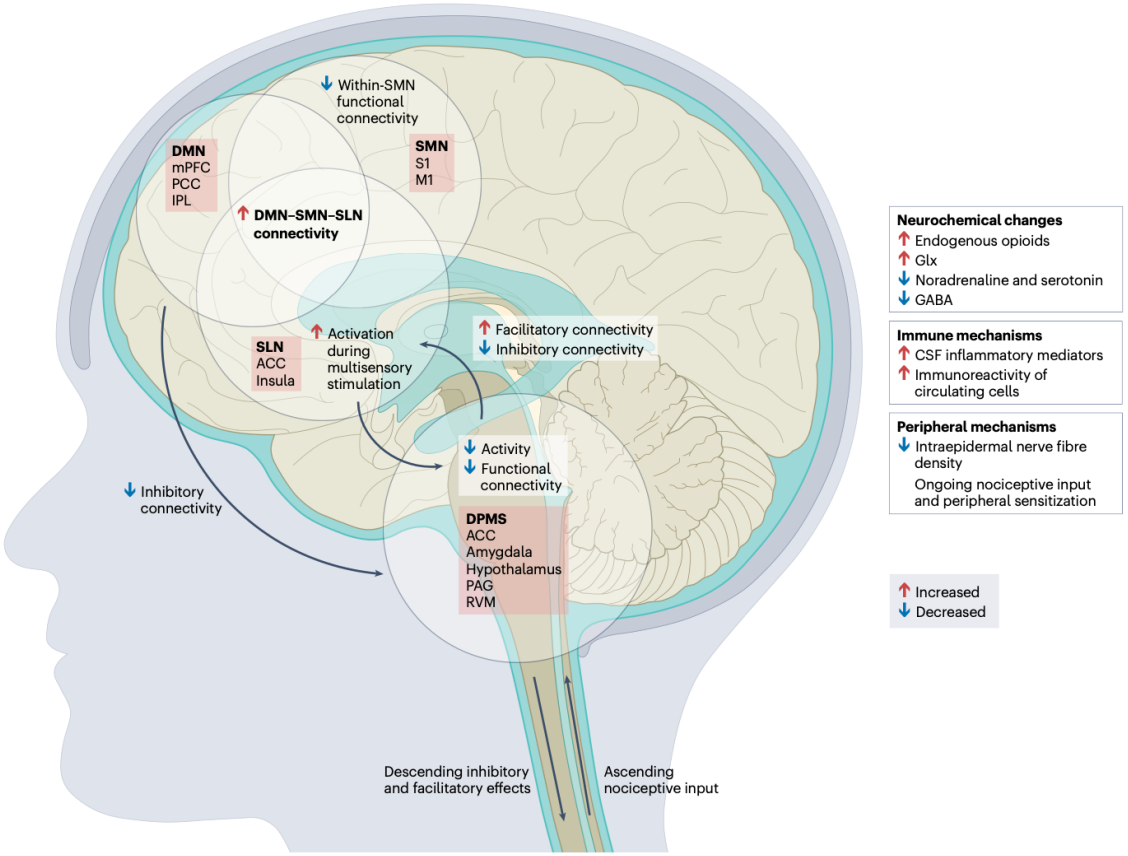


Figure 1-2. The pathophysiology of nociplastic pain.

Neuroimaging studies have shown abnormal brain connectivity in people with nociplastic pain. The spatial distribution of pain across the body is associated with increased functional connectivity between regions of the default mode network (DMN), salience network (SLN) and sensorimotor network (SMN) in pain conditions with presumed nociplastic mechanisms. In addition, people with nociplastic pain have altered activity within the descending pain modulatory system (DPMS), which modulates activity in the spinal dorsal horn and can have inhibitory or facilitatory influences on pain perception. Alterations in the immune system and peripheral nervous system are also observed in people with nociplastic pain. Future work is needed to understand how these systems interact in nociplastic pain states. ACC, anterior cingulate cortex; CSF, cerebrospinal fluid; GABA, γ-aminobutyric acid; Glx, glutamate + glutamine; IPL, inferior parietal cortex; M1, primary motor cortex; mPFC, medial prefrontal cortex; PAG, periaqueductal grey; PCC, posterior cingulate cortex; RVM, rostral ventromedial medulla; S1, primary somatosensory cortex. Reproduced with permission from Kaplan, Kelleher, et al. 2024[230]

1.2.4.1 Deficits in the descending pain Modulation system (DPMS)

The DPMS is central to the regulation of nociceptive input, functioning both to facilitate and inhibit pain signals depending on the context[27; 197]. At the core of the DPMS is the periaqueductal grey (PAG), a key hub that processes ascending nociceptive and descending cortical signals. The PAG, in conjunction with the rostral ventromedial medulla (RVM),

hypothalamus, amygdala, rostral and subgenual anterior cingulate cortex (ACC), and dorsolateral prefrontal cortex (dlPFC), exerts its modulatory effects at the spinal cord level[197; 243].

Individuals with nociplastic pain exhibit altered DPMS function. In fibromyalgia, neuroimaging studies show reduced functional connectivity within the DPMS during resting states[91; 360] and diminished activation during evoked pain, particularly in the rostral ACC, brainstem, and dorsal horn, suggesting reduced descending inhibition[57; 220]. In fibromyalgia, increased pain facilitation, which correlates with heightened pain sensitivity, has also been linked to increased connectivity between the PAG and RVM[190]. Meanwhile, structural changes, such as reduced grey matter volume, have also been reported in DPMS regions[105; 238; 329]. Neurochemical abnormalities, including elevated endogenous opioid levels and decreased μ-opioid receptor availability, contribute to reduced pain inhibition and opioid inefficacy[28; 191]. Meanwhile, decreased CSF levels of norepinephrine and serotonin align with the efficacy of treatments that enhance these neurotransmitters, such as serotonin-noradrenaline reuptake inhibitors (SNRIs) like duloxetine, and tricyclic antidepressants such as amitriptyline, in alleviating pain[93].

These deficits in the DPMS provide a potential mechanistic basis for the association between nociplastic pain and cognitive impairment. The overlap of regions involved in descending pain modulation and cognitive processing, including the PAG, ACC, and amygdala, underscores the importance of investigating this relationship. By exploring the functional and structural connectivity within the DPMS, in this thesis I examine its role in mediating the relationship between nociplastic pain and cognitive impairment. These

findings may inform therapeutic strategies for addressing the complex interplay between pain and cognition.

1.2.4.2 Resting state network connectivity changes

In nociplastic pain, the default mode network (DMN), salience network (SLN), and sensorimotor network (SMN) exhibit increased connectivity or "enmeshment"[83; 138; 210; 278; 333; 440]. Enhanced DMN–SLN–SMN connectivity is associated with greater pain intensity and widespread pain and may reflect a general marker of nociplastic mechanisms[25; 277; 333]. Evidence also suggests that connectivity changes may reverse following effective treatment, highlighting their potential role in tracking therapeutic outcomes treatment[192; 332].

1.2.4.3 Neurochemical imbalances

Increased excitatory neurotransmitter (glutamate/glutamine) concentration in the insula and posterior cingulate cortex and reduced inhibitory neurotransmitter (GABA) levels in the SLN are correlated with greater pain severity in fibromyalgia[193; 262; 353; 361]. These neurochemical changes may contribute to the observed network hyperconnectivity and heightened pain sensitivity.

Together, these findings demonstrate that nociplastic pain is associated with widespread disruptions in brain network function and neurochemistry. Understanding these alterations provides insights into the central mechanisms underlying pain, cognition, and sleep, the central themes of this thesis.

1.3 Cognitive impairments in fibromyalgia and nociplastic pain

Cognitive impairment is increasingly recognised as placing a significant burden among individuals with fibromyalgia and other nociplastic pain syndromes. Population-based studies have suggested an association between chronic pain and functional impairments, including frailty, increased risk of falls, and reduced independence in elderly adults[408; 436; 437]. These outcomes may be influenced, in part, by cognitive dysfunction among those with chronic pain[326; 408]. Cognitive impairment itself has limited therapeutic options, making the identification of modifiable risk factors particularly important for improving health outcomes[275].

In fibromyalgia, cognitive symptoms, or “fibro-fog”, are almost universally reported by patients[176]. Although population-based studies evaluating the prevalence of cognitive symptoms in fibromyalgia and other chronic pain conditions are limited, case-control studies consistently demonstrate a substantially higher prevalence of self-reported cognitive difficulties in fibromyalgia compared to other rheumatology populations. For example, Katz et al. found that 82% of fibromyalgia patients reported cognitive difficulties, with over half endorsing memory problems[232]. This was approximately 2.5 times more common than in a comparison group of rheumatology patients without fibromyalgia. Similarly, Leavitt et al. reported that 76% of fibromyalgia patients experienced cognitive symptoms, compared to 44% of other rheumatology patients[260].

Subjective cognitive symptoms are also reported in other chronic pain conditions, though at lower frequencies than in fibromyalgia. For instance, between one-fifth and one-quarter of patients with low back pain have self-reported cognitive difficulties[296],

while 3.3% of individuals with osteoarthritis endorsed frequent memory problems in a large cross-sectional study[211]. In another population-based study, 9.1% of patients with rheumatoid arthritis reported cognitive dysfunction[348].

Studies assessing objective cognitive performance in chronic pain conditions typically evaluate cognition along a continuum, which precludes estimates of categorical prevalence. Nonetheless, systematic reviews have demonstrated medium-to-large impairments in cognitive performance in fibromyalgia compared to healthy controls (effect size *g*= 0.87) [507]. The largest deficits have been observed in learning and memory (*g*= 0.94), and in attention and processing speed (*g*= 1.22), with medium effect sizes for working memory (*g*= 0.75) and executive function (*g*= 0.72). In chronic pain conditions more broadly, meta-analyses have identified moderate impairments in working memory and small-to-moderate impairments in executive function[48; 49]. Together, these findings indicate that cognitive difficulties are a significant burden in nociplastic pain conditions such as fibromyalgia. This is further reflected by their prioritisation as one of the top 10 research priorities for fibromyalgia in the James Lind Alliance initiative[158]. The moderate-to-large effect sizes observed in cognitive domains suggest that these impairments are not only statistically significant but may also have a meaningful impact on patients' quality of life.

1.3.1 Cognitive domains affected

Nociplastic pain is associated with impairments across several cognitive domains, including executive function, sustained attention, and memory, significantly impacting everyday functioning and quality of life in individuals.

1.3.1.1 Subjective cognitive complaints

Self-reported cognitive difficulties, often referred to as “brain-fog” or “fibrofog”, are commonly described by individuals with chronic pain conditions[326]. In fibromyalgia, these subjective complaints include difficulties with concentration and memory, forming a key component of the broader symptomatology of nociplastic pain[247].

1.3.1.2 Executive function

Executive function encompasses a set of higher-order cognitive processes, including working memory, cognitive flexibility, and self-regulation, that enable goal-directed behaviour[21; 171]. Individuals with fibromyalgia frequently report challenges in these areas, including poor concentration, forgetfulness, and reduced mental clarity[38], which may stem from the distracting effects of persistent pain and associated symptoms.

1.3.1.3 Sustained attention

Sustained attention, the ability to maintain focus over extended periods, may be particularly vulnerable in fibromyalgia. Evidence from conditions with similar symptoms, such as sleep deprivation and long COVID, suggests that deficits in sustained attention are clinically relevant, affecting activities such as driving, work, and education[131; 132; 226; 519; 520]. However, research into sustained attention in fibromyalgia remains relatively limited.

Sustained attention requires a dynamic interplay between bottom-up mechanisms (e.g., arousal maintenance and reorientation to targets) and top-down processes (e.g.,

task engagement and cognitive control)[89]. These mechanisms help address the dual challenges of filtering irrelevant information and sustaining focus over time. Common metrics for sustained attention include reaction time (RT), accuracy, and performance variability. Disruptions in this balance can result in state instability, where individuals oscillate between periods of focus ("in the zone") and attentional lapses ("out of the zone")[142]. Such lapses are marked by RT variability, which reflects an inability to maintain stable cognitive control[143; 384; 416].

Patients with fibromyalgia often experience severe sleep disturbances, high pain levels, and fatigue, all of which can exacerbate attentional deficits[88]. However, the specific contributions of these factors to sustained attention impairments remain poorly understood.

1.3.2 Evidence from population-based studies

1.3.2.1 Cross-sectional evidence

A 2018 systematic review of cross-sectional studies found consistent impairments across multiple cognitive domains in fibromyalgia compared to healthy adults[38]. The largest deficits were observed in executive function, including tasks related to set-shifting, accessing, and updating information, followed by smaller deficits in processing speed, and both short- and long-term memory. This highlights the broad cognitive impact of fibromyalgia on various mental processes.

In an analysis of chronic pain, two systematic reviews by Berryman et al. found that individuals with chronic pain consistently performed worse than healthy controls on tasks requiring complex executive function[48; 49]. Memory task performance, in both

accuracy and response times, was also impaired. Of chronic pain conditions, fibromyalgia patients displayed the most significant deficits.

1.3.2.1.1 Limitations and gaps in cross-sectional research

While these cross-sectional studies provide evidence of a cross-sectional association between chronic pain and cognitive impairment, they do not establish causality. The temporal relationship—whether pain leads to cognitive deficits and decline—remains unclear.

1.3.2.2 Evidence for cognitive decline in chronic pain

Although chronic pain is linked to an increased dementia risk[514], its impact on specific cognitive domains, such as executive function, or measurable cognitive decline remains uncertain. This question is important, as cognitive impairments associated with chronic pain can affect daily functioning, decision-making, and quality of life, even in the absence of dementia. A literature review summarised in **Table 1-1** (see Appendix F for search strategy) identified 16 studies exploring this longitudinal association[37; 40; 204; 208; 240; 292; 308; 370; 377; 385; 391; 446; 447; 462; 470; 492].

Whitlock et al. conducted one of the first large-scale prospective studies on the topic in 10,065 older US adults[492]. Persistent pain was associated with a 9.2% more rapid decline in memory scores over 8.6 years. However, this study did not assess other cognitive domains such as executive function, and lacked detailed characterisation of pain or factors such as analgesia use.

Similarly, Van der Leeuw et al. found pain severity was associated with impaired memory performance, but not with executive function or attention, over a 2.75-year

follow-up[462]. Bell et al. observed significant declines in cognitive performance, particularly memory, in individuals with persistent pain and pain interference over 18 years[36]. In contrast, Veronese et al. found no association between pain and declines in memory, verbal fluency, or processing speed over four years. Although the study's high attrition rate and adjustments for potential mediators such as depression likely attenuated results[470]. Similarly, Rouch et al. reported no significant associations between chronic pain and decline in most cognitive domains, apart from psychomotor speed, which declined more rapidly in pain sufferers[385].

Although Zhao et al. found a relationship between multi-site chronic pain and age-related cognitive decline in UK Biobank, a key limitation lies in their assessment of cognition at a single time point[522]. The authors inferred cognitive decline by analysing age-related trajectories within cross-sectional data rather than observing longitudinal changes in individual cognition over multiple time points. This design conflates inter-individual variability with intra-individual change, which limits its ability to draw robust conclusions about cognitive decline over time. This underscores the need for studies with repeated cognitive assessments to validate these findings.

Smaller studies, such as those by Milani et al. and Honda et al., further highlight variability in findings. Milani identified an association between untreated and treated pain interference and cognitive impairment in Mexican adults, partially mediated by depressive symptoms[308]. Honda found chronic pain was associated with increased odds of cognitive impairment in older Japanese adults with disabilities, but did not adjust for educational attainment, which may influence results[203].

There are several potential explanations for the conflicting findings. Most studied elderly cohorts, however it may be that the cumulative burden of exposure to pain across middle life, rather than later life, is important in the development of cognitive impairment. Methodological heterogeneity, including differences in pain definitions, cognitive outcomes, follow-up duration, and adjustment for confounders, further complicate synthesis. Most studies adjust for key confounders, including age, sex, and education, as well as common medical comorbidities such as diabetes, hypertension, and cardiovascular disease. Lifestyle factors such as smoking, alcohol use, physical activity, and BMI are also frequently included, along with depression, which is closely linked to both pain and cognition. However, adjustments for socioeconomic factors such as income and social deprivation, are less consistent. Importantly, factors like sleep disturbance, depression, and analgesia use may more appropriately be considered mediators, as they likely lie on the causal pathway between pain and cognitive outcomes. Similarly, medical comorbidities may also function as mediators rather than confounders, further complicating interpretation of these associations. Analysis strategies that distinguish between confounders and mediators are essential for clarifying the relationships in this field. Importantly, few studies have examined mechanisms linking pain and cognition, such as altered pain processing and DPMS function.

Addressing these unanswered questions is critical, particularly given the modifiability of chronic pain. This thesis aims to bridge these gaps by exploring nociplastic pain's role in cognitive decline, with a focus on sleep and DPMS function as potential mediators and targets for intervention.

Author (year)	Study population	Follow-up (years)	Pain definition	Pain cases (N)	Measure of cognition	Risk of adverse cognitive outcomes (after adjustment)		Cognitive decline?	Comments
Rist (2011)[370]	1,170 adults in Epidemiology of Vascular Ageing study, France (mean age: no headache, 68.9; migraine, 69; non-migraine headache, 69.3. 58.4% female)	4-5	Migraine or non-migraine headache	Migraine: 167 (14.3%). Non-migraine headache: 65 (5.6%)		Non-migraine headache	Migraine	**No**	Headache not associated with cognitive decline. Results for group-by-time interaction given. Cognitive decline defined as being in bottom decile of change score.
					MMSE	P=0.68	P=0.85		
					Wechsler	**P=0.44**	**P=0.02**		
					TMT-A	P=0.84	P=0.76		
					TMT-B	P=0.34	P=0.83		
					Rey	P=0.36	P=0.12		
					Raven	P=0.22	P=0.42		
					Benton	P=0.14	P=0.67		
					Finger Tapping	P=0.85	P=0.43		
					Word Fluency	P=0.60	P=0.36		
					Cognitive decline	OR 0.88 (95%CI: 0.39–2.01)	OR 0.76 (95%CI: 0.42–1.37)		
Whitlock (2017)[492]	10,065 adults ≥62 living in the community, enrolled in Health and Retirement Study, USA (median age 73; 60% female)	Pain group: 8.6 (95%CI 4, 12.1) Comparison group: 11.8 (95%CI 6.3, 12.2)	Persistent moderate or severe pain (over 2 years)	1,120 (11.1%)	**Memory score**	**9.2% (95%CI 2.8, 15.0)** more rapid decline in memory score in pain group[1]		**Yes**	Persistent pain associated with faster decline in memory score. No information about source or type of pain.
van der Leeuw (2018)[462]	441 adults ≥65 years enrolled in Central Control of Mobility in Aging study, USA (mean age 76; 55.8% female)	2.71 (range 0-6.16)	Pain severity (NRS)	Moderate/severe pain (NRS 5-8): 285 (64.6%). Severe pain (NRS 9-20): 78 (17.7%)	Attention (*impairment defined as a score >1 SD below baseline mean*)	HR 1.00 (95%CI 0.91, 1.09, P=0.942)		**Yes**	Association between pain severity NRS and memory impairment. No information about duration, source or type of pain.
					Executive function	HR 1.05 (95%CI 0.97, 1.13, P=0.201)			
					Memory	**HR 1.14 (95%CI 1.05, 1.24, P=0.002)**			
Veronese (2018)[470]	6,515 adults ≥50 years living in community enrolled in English Longitudinal Study of Ageing, UK (mean age 65; 57.3% female)	4	Presence of pain; mild, moderate, severe pain	Any pain: 2,317 (35.6%). Mild: 679 (10.4%). Moderate: 1,166 (17.9%).	Verbal fluency score	Change in score: Any pain: β 0.02 (95%CI -0.15, 0.18, P=0.85) Mild: β 0.07 (95%CI -0.38, 0.53, P=0.75) Moderate: β -0.18 (95%CI -0.58, 0.23, P=0.39)		**No***	*Severe pain associated with worse memory at follow-up. No other significant associations. No details on source or type of pain. No measure of analgesia use

Author (year)	Study population	Follow-up (years)	Pain definition	Pain cases (N)	Measure of cognition	Risk of adverse cognitive outcomes (after adjustment)	Cognitive decline?	Comments
				Severe: 450 (6.9%)		Severe: β 0.06 (95%CI -0.57, 0.69, P=0.85)		
					Memory score	β 0.05 (95%CI -0.28, 0.38, P=0.77) Mild: β 0.02 (95%CI -0.22, 0.25, P=0.89) Moderate: β 0.05 (95%CI -0.16, 0.26, P=0.63) Severe: β -0.36 (95%CI -0.68, -0.04, P=0.04)		
					Processing speed score	β 0.55 (95%CI -18.4, 2.93, P=0.65) Mild: β 3.02 (95%CI -6.55, 12.59, P=0.54) Moderate: β -0.08 (95%CI -8.53, 8.38, P=0.99) Severe: β 0.82 (95%CI -12.32, 13.95, P=0.90)		
Martins (2020)[292]	275 adults in Portugal (mean age 70.4; 64% female)	5	Migraine, non-migraine headache	Migraine: 35 (12.7%). Non-migraine headache: 24 (8.7%)	**Executive function**	**F=4.094; P=0.018**	**Yes***	Headache associated with small decline in executive function, but not other domains. Scores are the sum of individual cognitive tests within each domain. Cognitive impairment defined as 1.5 SD on composite of executive function and memory. Group-by-change ANCOVA result reported.
					Memory	F=0.398, P=0.69		
					Cognitive impairment	Migraine: OR 0.65 (95%CI 0.13, 3.16). Non-migraine: OR 0.927 (95%CI 0.24, 3.6)		
Huai 2021[208]	134 adults >65 years undergoing hip replacement surgery in China	2 months	Chronic pain *(Pain ≥4 on VAS for 3+ months)*	61 (43.2%)	Post-operative cognitive dysfunction at 2 months (decrease of >1.96 SD in ≥2 cognitive tests)	OR 1.387 (95%CI 0.152, 12.681); P=0.772	**No**	Pre-operative chronic pain not associated with post-operative cognitive decline at 2 months. Significant increase in post-operative cognitive dysfunction at 7 days.
Rong (2021)[377]	6,869 adults ≥50 in English Longitudinal Study of Ageing (mean age 63.9; 56.7% female)	12	Pain intensity NRS; Episodic pain; Persistent pain	Episodic pain: 1,114 (16.2%). Persistent pain: 869 (12.7%)		Per 5-point increase in pain / Episodic pain / Persistent pain	**Yes**	Pain intensity associated with cognitive decline. Pain-by-time interaction reported for pain intensity NRS. Mean difference in rate of change reported for episodic and persistent pain. Global scores computed by average of individual test scores
					Global cognitive score	**β -0.009 (95%CI -0.013, -0.006); P<0.001** / **β -0.01 (95%CI -0.021, -0.001); P<0.001** / **β -0.031 (95%CI -0.043, -0.018); P<0.001**		
					Verbal memory	**β -0.006 (95%CI -0.009, -** / **β -0.007 (95%CI -0.013, -** / **β -0.025 (95%CI -0.033, -**		

Author (year)	Study population	Follow-up (years)	Pain definition	Pain cases (N)	Measure of cognition	Risk of adverse cognitive outcomes (after adjustment)			Cognitive decline?	Comments
						0.004); P<0.001	**0.001); P<0.001**	**0.017); P<0.001**		
					Semantic fluency	**β -0.007 (95%CI -0.009, -0.004); P<0.001**	**β -0.009 (95%CI -0.017, -0.002); P<0.001**	**β -0.025 (95%CI -0.033, -0.017); P<0.001**		
					Temporal orientation	**β -0.007 (95%CI -0.011, -0.003); P<0.001**	**β -0.01 (95%CI -0.021, -0.000); P<=0.001**	**β -0.019 (95%CI -0.032, -0.005); P=0.001**		
Rouch (2021)[385]	693 adults ≥65 living in France enrolled in PAQUID study	12 (range 3-12)	Chronic pain *(moderate or intense daily pain for 6+ months)*	234 (33.8%)	Global cognition	β -0.037 (SE 0.026) P=0.157			**Yes***	Chronic pain marginally significant associated with decline in psychomotor speed. Factorial invariance of latent variable for global cognition not reported.
					MMSE	β 0.015 (SE 0.057) P=0.79				
					Short-term visual memory (BVRT)	β 0.008 (SE 0.053) P=0.88				
					Language skills and executive function (IST)	β 0.006 (SE 0.058) P=0.92				
					Psychomotor speed (DSST)	**β -0.191 (SE 0.085) P=0.024**				
					Associative memory (WPAT)	β -0.122 (SE -0.128) P=0.34				
					Selective attention (ZCT)	β 0.097 (SE 0.081) P=0.23				
Terassi (2021)[446]	104 adults ≥60 living in Sao Brazil, Brazil	4	Chronic pain *(continuous or recurrent pain for 6+ months).* Pain intensity *(NRS, 0-10)*	73 (70.2%)		Chronic pain	Pain intensity		**No**	No association between chronic pain and cognitive decline. Did not account for socio-economic deprivation.
					ACE-R Total	β 0.03 (95%CI 4.23, 4.30) P=0.99	β 0.03 (95%CI -0.67, 0.74) P=0.93			
					Attention/orientation	β -0.34 (95%CI -1.33, 0.65) P=0.49	β 0.07 (95%CI -0.10, 0.23) P=0.44			
					Memory	β -0.27 (95%CI -2.59, 2.05) P=0.82	β -0.17 (95%CI -0.56, 0.22) P=0.38			
					Verbal fluency	β 0.63 (95%CI -0.48, 1.74) P=0.26	β 0.10 (95%CI -0.09, 0.28) P=0.28			
					Language	β 0.59 (95%CI -0.98, 2.16) P=0.46	β 0.11 (95%CI -0.17, 0.38) P=0.44			
					Visuospatial skills	β -0.57 (95%CI -1.72, 0.58) P=0.33	β -0.07 (95%CI -0.24, 0.11) P=0.46			

Author (year)	Study population	Follow-up (years)	Pain definition	Pain cases (N)	Measure of cognition	Risk of adverse cognitive outcomes (after adjustment)		Cognitive decline?	Comments
Bell (2022a)[39]	2,144 adults ≥60 in Puerto Rican Elderly Health Conditions study (mean age 69.5; 62.7% female)	4	Persistent pain *(pain at baseline and follow-up).* New pain (*no pain at baseline, pain at follow-up*). Recovered pain *(Pain at baseline, no pain at follow-up).*	789 (36.8%)	Cognitive decline on Mini Mental Cabán	Persistent pain: β -0.04 (95%CI -0.15, 0.07); P=0.481 **New pain: β 0.16 (95%CI 0.06, 0.26); P=0.001** Recovered pain: β 0.05 (95%CI -0.13, 0.23); P=0.685		**Yes**	New-onset pain associated with cognitive decline. Persistent and new-onset pain also associated with incident subjective memory problems.
Bell (2022b)[40]	8,515 adults ≥65 in HRS in USA (mean age 74.2 years; 59.2% female)	18	Persistent pain, and persistent pain interference	2,138 (25.8%)		Persistent pain	Persistent pain interference	**Yes**	Persistent pain and pain interference associated with cognitive decline. Association strongest with memory subdomains. No association with pain intensity
					Cognitive performance, 0-35 *(included tests of episodic memory, attention/processing speed, and vocabulary)*	**β -0.48 (95%CI -0.65, -0.32) P<0.001**	**β -0.38 (95%CI -0.56, -0.23) P<0.001**		
					Cognitive impairment *(>1.5 SD below mean)*	**OR 1.31 (95%CI 1.18, 1.45) P<0.001**	**OR 1.21 (95%CI 1.07, 1.37) P=0.003**		
Sadlon (2023)[392]	995 adults from ADNI cohort (mean age 73; 43.7% female)	2	Persistent or recurrent pain lasting >3 months	605 (60.8%)	Composite scores for memory (ADNI-MEM) and executive function (ADNI-EF)	No significant association (individual results not presented)		**No**	Chronic pain was linked with increased biomarkers of neurodegeneration but did not lead to observed cognitive decline over 24 months. Short follow-up limits assessment of long-term cognitive impacts.
Zhao (2023)[522]	354,943 adults in UK Biobank in Great Britain (mean age 56.8; 52.7% female)	N/A	Single-site and multi-site chronic pain (*3+ months*)	Single site: 76,206 (21.5%) Multi-site: 89,991 (25.4%)		Single-site pain	Multi-site pain	**Yes**	Cognitive performance variables only assessed at one timepoint (UK Biobank Imaging visit); association presented is slope between age and performance. Also found multi-site chronic pain associated with smaller hippocampal grey matter volume.
					Fluid intelligence	F=0.701, P=0.363	F=0.191, P=0.662		
					Numeric memory	F=0.029, P=0.864	**F=6.957, P=0.008**		
					Trail Making Test (B)	F=0.168, P=0.682	**F=8.412, P=0.004**		
					Matrix Pattern Completion	F=0.570, P=0.418	F=1.198, P=0.215		
					Symbol Digit Substitution	F=0.902, P=0.343	F=0.007, P=0.932		
					Paired associate learning	F=1.217, P=0.199	F=3.205, P=0.073		

Author (year)	Study population	Follow-up (years)	Pain definition	Pain cases (N)	Measure of cognition	Risk of adverse cognitive outcomes (after adjustment)		Cognitive decline?	Comments
					Prospective Memory	F=2.628, P=0.105	F=2.242, P=0.107		
Kim (2024)[240]	3,287 adults ≥60 with baseline MMSE ≥24 in Korea (mean age 67.6; 46% female)	Up to 14	Pain (*no timeframe given*). Pain interference (*limitation of ADLs by pain*)	2,261 (68.8%	**Korean MMSE**	Pain **β -0.17 (95%CI -0.243, -0.097)**	Interference **β -0.315 (95%CI -0.392, -0.237)**	**Yes**	Pain associated with decline in MMSE scores. Pain-by-time result reported. No time-frame reported for pain definition. Did not adjust for baseline MMSE score
Milani (2024)[308]	313 adults ≥80 in Mexico (mean age 84.8 years; 59.7% female)	6 years	Pain interference (*untreated and treated*)	Pain interference (treated): 122 (39%). Pain interference (untreated): 24 (7.7%)	**MMSE <21**	Pain interference (treated): **OR 1.99 (95%CI 1.15, 3.44) P=0.014**	Pain interference (untreated): **OR 2.18 (95%CI 1.09, 4.36) P=0.028**	**Yes**	Pain interference associated with lower MMSE score. Association partially mediated by depressive symptoms
Honda (2025)[203]	102 adults ≥65 with disabilities in Japan (median age 86 years; 69.6% female)	2 years	Chronic pain (*3+ months*)	46 (45%)	**MMSE <24**	**OR 4.1 (95%CI 1.46, 11.57) P=0.008**		**Yes**	Chronic pain associated with lower MMSE score. Did not adjust for educational attainment

Author (year)	Study population	Follow-up (years)	Pain definition	Pain cases (N)	Measure of cognition	Risk of adverse cognitive outcomes (after adjustment)	Cognitive decline?	Comments
Adjustment for confounding:								
Rist (2011): Adjusted for age, gender, education (age completed), and smoking status.								
Whitlock (2017): Adjusted for age, sex, race, highest level of education, smoking, medical comorbidities (hypertension, diabetes, cancer, chronic lung disease, heart disease, stroke). Additional adjustment for potential mediators: household financial assets, marital status, alcohol use, depressive symptoms, limitations of activities of daily living.								
Van der Leeuw (2018): Adjusted for age, sex, ethnicity, years of education, medical comorbidities (diabetes, heart failure, arthritis, hypertension, major depression, stroke, Parkinson's disease, chronic obstructive pulmonary disease, angina, myocardial infarction), depressive symptoms, psychiatric medication and analgesia use.								
Veronese (2018): Adjusted for age, sex, race, education (formal college vs other), marital status, smoking, activities of daily living, body mass index, physical activity, alcohol use, depressive symptoms, household wealth, comorbidities (osteoarthritis, osteoporosis, stroke, heart problems, lung diseases, cancer, diabetes, hypertension, Parkinson's disease), and baseline cognition.								
Martins (2020): Adjusted for age at follow-up, gender, baseline cognitive score, depressive symptoms.								
Huai (2021): Adjusted for BMI, pain period, diagnosis, surgery type, length of hospital stay, intraoperative hypotension, intraoperative ephedrine use, postoperative NSAID use, postoperative pain VAS.								
Rong (2021): Adjusted for baseline age, sex, body mass index, pain medication intake, education, marital status, current smoking, alcoholic drink, physical activity, depressive symptoms, hypertension, diabetes, coronary heart disease, stroke, chronic lung disease, asthma and cancer.								
Rouch (2021). Adjusted for age, sex, educational level, depressive symptoms, opioid and antidepressant use, and number of comorbidities.								
Terassi (2021). Adjusted for age, sex, educational level, depressive symptoms, smoking status, current alcohol use, number of comorbidities.								
Bell (2022a): Adjusted for age, gender, education, diabetes, cardiovascular conditions (myocardial infarction, hypertension, congestive heart failure, chronic lung disease, and arthritis.								
Bell (2022b). Adjusted for age, sex, educational level, household income, depressive symptoms, number of comorbidities.								
Zhao (2023). Adjusted for age, sex, ethnicity, educational level, social deprivation, BMI, smoking status, alcohol consumption, depression, cancer, diabetes, heart disease (angina, hypertension, heart attack, stroke).								
Kim (2024): Adjusted for sex, age at the first wave, education level, marital status, employment status, comorbidities, smoking, alcohol consumption, and physical activity.								
Milani (2024). Adjusted for age, sex, language, educational level, marital status, depressive symptoms, medical comorbidities (diabetes, stroke, cancer, hypertension, arthritis).								
Honda (2025). Adjusted for age, sex, BMI, number of household members, levels of care, number of medications, depression, functional comorbidity index, time up and go test, five-standing test, one-leg standing time, malnutrition, and sleep disorder, cognitive impairment at baseline.								
Abbreviations: ACE-R, Addenbrooke's Cognitive Examination Revised; BVRT, Benton Visual Retention Test; CI, confidence interval; CP, chronic pain; DSST, Digit Symbol Substitution Test; EF, executive function; HR, hazard ratio; IQR, interquartile range; IST, Isaacs Set Test; MMSE, Mini-Mental State Examination; NRS, Numeric Rating Scale; NY, New York; OR, odds ratio; PAQUID, Personnes Agées Quid; SD, standard deviation; SF-36, Short Form-36; UKB, UK Biobank; USA, United States of America; Wald, Wald test statistic; WPAT, Wechsler Paired-Associates Test; ZCT, Zazzo's Cancellation Task.								

Table 1-1. Overview of prospective cohort studies of pain and adverse cognitive outcomes identified for narrative review.

Sixteen longitudinal studies which examined pain and performance on cognitive tests over time were included. Cross-sectional studies and studies evaluating dementia as an endpoint were excluded, as dementia occurrence is not the primary focus of this thesis. See Appendix F.1 for search strategy and study selection flow diagram (Supplementary Figure F-1).

1.3.3 Mechanisms linking pain and cognitive decline

A direct association between chronic pain and cognitive impairment is hypothesised to involve three key mechanisms[326]: competition for limited neural resources[184], structural and neurochemical changes[184], and dysregulated neurotransmitter balance[259]. However, as outlined above, other factors such as sleep disturbance may mediate these associations.

1.3.3.1 Competition for neural resources

Chronic pain may disrupt cognition by monopolising attentional resources, reducing the capacity available for other cognitive tasks[466]. Pain intensity, distribution, and qualities influence this cognitive burden, particularly with respect to sustained attention. Studies in fibromyalgia patients have shown that pain diverts cognitive resources, resulting in increased reaction time variability and worse accuracy on a vigilance task[127]. The impact of pain is more pronounced when assessed contemporaneously with cognitive tasks but diminishes with increasing temporal distance, supporting the idea that pain is disruptive during the task itself[126; 167]. Impaired sustained attention has also been shown in neuropathic pain conditions, further highlighting the cognitive toll of pain[215]. These findings underscore the importance of timing and context in evaluating the relationship between pain and cognition.

1.3.3.2 Structural and neurochemical changes

Chronic pain induces structural changes in brain regions critical for cognition, such as the prefrontal cortex (PFC) and amygdala, which exhibit reductions in grey matter

volume in fibromyalgia and other chronic pain conditions[184]. Dysregulated neurochemistry, including imbalances in GABA, further contributes to impaired executive function[259]. These changes not only disrupt nociceptive processing but may also impair cognitive processes such as attentional control and emotional regulation. Disrupted DPMS function has broader implications for cognition, particularly executive function. The PAG modulates higher cortical control of pain through attentional mechanisms, and disruption to this pathway may impair attentional flexibility and other cognitive processes[452].

1.3.3.3 Psychological factors & sleep disturbances

Pain-related cognitive impairments may also be mediated by psychological factors, such as depression and anxiety, and by sleep disturbances. Sleep disruption, a hallmark of nociplastic pain, exacerbates cognitive deficits, particularly in attention and executive function[88]. These disruptions create a feedback loop in which poor sleep and emotional dysregulation amplify pain perception, worsening the overall cognitive burden.

1.3.3.4 Analgesia use

Analgesics have a complex relationship with cognition, acting as both potential mitigators and drivers of cognitive impairment. Opioids, for instance, have been associated with small declines in cognitive function in older adults[482] but are also linked to improvements in some contexts[234; 351]. Gabapentinoids, commonly prescribed for neuropathic pain, are associated with cognitive difficulties, particularly in older populations[339]. Similarly, tricyclic antidepressants like amitriptyline, often used for both depression and pain management, have been linked to cognitive

dysfunction in patients with postherpetic neuralgia[355] and depression[148; 444]. These findings underscore the importance of considering medications when studying the pain-cognition relationship.

1.4 **Sleep, pain, and cognition**

Sleep disturbances may be an important factor linking pain and cognitive dysfunction. Understanding the interplay between these domains provides insight into the mechanisms underlying cognitive deficits in chronic pain populations and highlights the potential for targeted interventions.

1.4.1 Sleep disturbances in nociplastic pain

Sleep disturbances are highly prevalent in fibromyalgia, with up to 90% of patients reporting poor sleep quality, difficulty initiating or maintaining sleep, and non-restorative sleep[88]. These disturbances often co-occur with heightened pain sensitivity and cognitive impairments, forming a feedback loop that exacerbates symptom severity[88]. As outlined in Section 1.2.3.5, sleep disturbance, particularly disruption to deep NREM sleep, is associated with onset of the cardinal features of nociplastic pain such as widespread musculoskeletal pain, fatigue, and mood disturbance. Poor sleep is not only associated with greater pain intensity but also with deficits in attention, memory, and executive function. For example, subjective sleep quality has been linked to attentional impairments[177], while chronic sleep disruption in fibromyalgia is associated with greater lapses in attention and reduced cognitive flexibility[313].

1.4.2 Sleep as a mediator

Sleep may play a mediating role in the relationship between pain and cognition through its effects on both pain and cognitive processing. Acute sleep deprivation has well-documented impacts on sustained attention, leading to increased reaction time variability, slower responses, and higher error rates on attention tasks[226; 290]. These effects are particularly pronounced in tasks requiring sustained focus, such as the Psychomotor Vigilance Test (PVT) or Attention Network Test (ANT), likely due to the susceptibility of visual attention to sleep pressure[128]. Indeed, sleep deprivation exerts more significant effects on sustained attention than on other cognitive domains, such as working memory[130; 132].

At the population level, both short and long sleep durations demonstrate U-shaped relationships with cognitive performance and decline[281; 442; 496; 510]. Short sleep is associated with insufficient restorative processes, impairing memory consolidation and attention, while long sleep is more commonly linked to disrupted sleep architecture[33].

1.4.3 Therapeutic Implications

Sleep represents a promising therapeutic target for mitigating both nociplastic pain and its associated cognitive dysfunction, providing a dual benefit of improving pain and cognitive performance (**Figure 1-3**).

1.4.3.1 Non-pharmacological interventions for sleep in chronic pain

Non-pharmacological interventions such as cognitive behavioural therapy for insomnia (CBT-I) have shown efficacy in improving sleep in chronic pain populations[443]. These

treatments not only improve sleep quality but, in some studies, also have downstream benefits on pain intensity, mood, and fatigue, suggesting that interventions targeting sleep could enhance overall quality of life for individuals with fibromyalgia.
Several studies have shown that face-to-face CBT-I improves sleep quality in fibromyalgia, but high attrition limits conclusions about its long-term benefits.

1.4.3.2 Digital CBT-I

Digital CBT-I (dCBT-I) offers a scalable and accessible alternative to face-to-face therapy, making it particularly attractive in conditions like fibromyalgia, where barriers to in-person treatment are common. Evidence suggests that dCBT-I achieves comparable benefits in subjective sleep quality to face-to-face CBT-I[516].
Small pilot studies of dCBT-I in chronic pain conditions have shown encouraging results(Crawford, Luik et al. 2020)[488; 518]. However, these studies relied on close participant observation, with frequent investigator contact, which may inflate engagement rates.

Despite promising pilot results, RCTs of dCBT-I tools such as *Sleepio* in chronic pain populations are lacking. In insomnia, however, large RCTs have established *Sleepio's* efficacy. For example, Espie et al. observed sustained benefits in sleep quality and quality of life at six months[139]. The DISCO trial demonstrated that *Sleepio* improved subjective dyscognition, mediated by enhanced sleep quality. However, no improvements were observed in objective cognitive measures, likely due to the insensitivity of the UK Biobank cognitive battery used in the study[253]. This limitation

underscores the need for more sensitive cognitive assessments capable of detecting subtle differences in cognition[520].

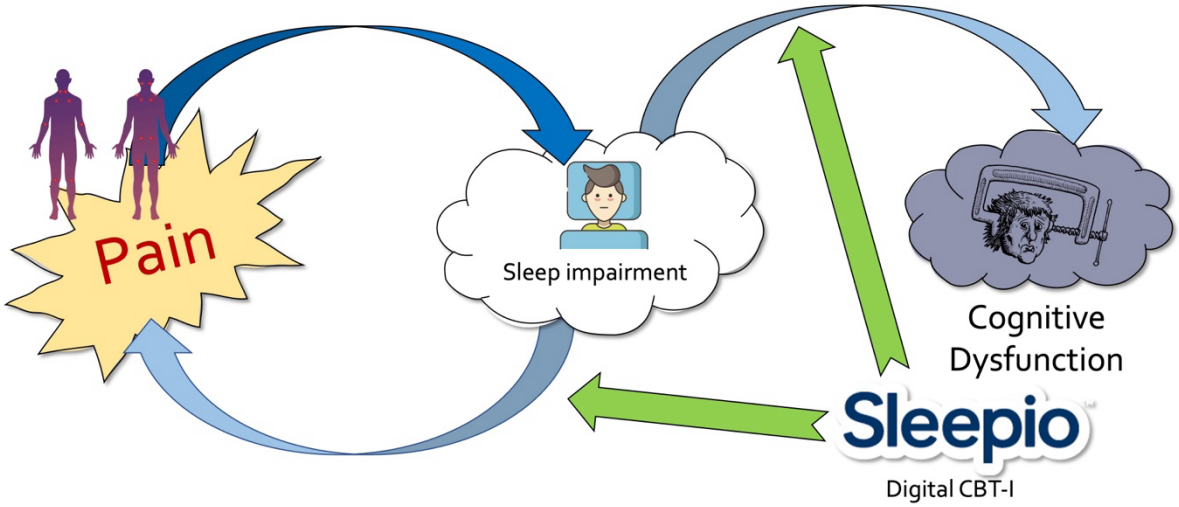


Figure 1-3. Digital CBT-I may improve cognitive impairment in fibromyalgia.

CBT-I, cognitive behavioural therapy for insomnia.

1.5 Research gaps and thesis objectives

Significant gaps remain in understanding the relationship between nociplastic pain, sleep disturbances, and cognitive impairment. The mechanisms linking fibromyalgia and cognition are not well-understood, and the role of sleep as a mediator is underexplored. Furthermore, while non-pharmacological interventions like CBT-I show promise in improving sleep, their impact on cognitive outcomes in fibromyalgia remains unclear.

The aim of this thesis is to investigate the relationship between fibromyalgia, nociplastic pain, and cognitive impairment, with a particular focus on sleep disturbances. This is achieved through two key studies: an epidemiological study of nociplastic pain and cognition in UK Biobank, a large population-based cohort study of middle-age British adults; and an observational study evaluating sustained attention in patients with fibromyalgia, with an embedded feasibility trial of digital CBT-I (PainLESS).

The thesis is structured as follows: **Chapter 2** presents a systematic review and meta-analysis of pharmacological and non-pharmacological therapies for sleep in fibromyalgia. **Chapter 3** investigates the cross-sectional and longitudinal relationship between nociplastic pain severity and executive function in UK Biobank, with an evaluation of potential mediators such as sleep disturbances. **Chapter 4** explores DPMS connectivity in UK Biobank, focusing on its role in mediating the relationship between nociplastic pain severity and executive function. **Chapter 5** describes the PainLESS study, a feasibility trial for dCBT-I, aiming to assess its impact on sleep and cognitive outcomes. **Chapter 6** examines observational data from PainLESS to analyse the association between fibromyalgia symptom severity and sustained attention, comparing results with healthy controls. Finally, **Chapter 7** summarises the findings, discusses their clinical significance, and outlines future research directions.

1.5.1 Aims and Objectives

- Explore the interplay between nociplastic pain, sleep, and cognition.
- Identify potential mediators and pathways.
- Evaluate feasibility of dCBT-I as a therapeutic approach.

This thesis tests the following hypotheses: nociplastic pain severity and fibromyalgia are associated with worse cognitive performance. Nociplastic pain severity is linked to greater cognitive decline at the population level. A trial of dCBT-I is feasible in fibromyalgia.

By addressing these hypotheses, this thesis aims to bridge important knowledge gaps and provide a foundation for targeted therapeutic interventions to improve cognitive outcomes for individuals with fibromyalgia.

2 *Chapter Two: Treatments for sleep in fibromyalgia: a systematic review and meta-analysis*

2.1 Introduction

Fibromyalgia is a debilitating chronic pain condition characterised by chronic widespread pain accompanied by sleep difficulties, cognitive impairment, mood disturbance, and fatigue[22; 153; 399]. Sleep disturbance is central to fibromyalgia, as recognised by its inclusion in the 2016 diagnostic and classification criteria[15; 136; 499-501]. There is a bidirectional relationship between sleep disturbance and pain, with sleep issues potentially contributing to the aetiology of fibromyalgia rather than being a consequence[88]. This is supported by epidemiological and neuroimaging studies[110; 246], underscoring the potential of addressing sleep disturbance as a therapeutic target.

The James Lind Alliance Priority Setting Partnership emphasises the importance of improving management of sleep disturbance in fibromyalgia[158]. However, current clinical guidance for the management of sleep disturbance in fibromyalgia lack clear consensus[1; 50; 283]. The most recent guidance from the European Alliance of Associations for Rheumatology (EULAR) recommend meditative movement, amitriptyline, cyclobenzaprine and pregabalin to improve sleep in the context of fibromyalgia[283]. However, apart from amitriptyline, none of these therapies were recommended by the UK's National Institute for Health and Care Excellence (NICE) 2021 guidelines for the

management of chronic pain (NG193[2]), and further research on cognitive behavioural therapy for insomnia (CBT-I) was encouraged.

CBT-based approaches have a substantial evidence base to support their effectiveness in improving quality of life, physical and mental health for people living with a range of physical and psychological health problems[162], but its effectiveness at improving sleep in fibromyalgia is less certain. CBT-I is recommended as the first-line treatment for insomnia, with hypnotic medication to be considered only if CBT-I does not work[362]. However, despite strong evidence supporting the effectiveness of CBT-I in primary insomnia, its availability is limited due to a lack of trained professionals[92; 120].

The aim of this systematic review is to identify and synthesise the current evidence on the effectiveness of pharmacological and CBT therapies in improving sleep quality in people with fibromyalgia.

2.2 Methods

2.2.1 Search strategy and selection criteria

A systematic review was conducted in accordance with the strategy recommended by the Cochrane Collaboration handbook[114]. Searches were conducted across PubMed, MEDLINE, Embase, Cochrane CENTRAL, and CINAHL, using keywords related to pharmacological treatments or CBT in fibromyalgia (**Appendix A.1**). The search was performed to include studies published up to April 2023. Additional records were identified through a snowball search of references and clinical trial registries. Duplicates were removed, and the title and abstracts of remaining articles were reviewed by four researchers to identify studies suitable for inclusion based. The full texts of remaining articles were reviewed by the same researchers to determine their relevance. After this, four authors independently reviewed all resulting papers for eligibility. Discrepancies were resolved through discussion at each stage and consensus was achieved.

Inclusion criteria:

1. Original research from randomised controlled trials. Non-randomised trials and observational studies were excluded.
2. Published in English or translated to English.
3. Participants with a diagnosis of fibromyalgia based on the American College of Rheumatology 1990, 2010 or 2016 diagnostic criteria[499], the ACTTION-APS Pain

Taxonomy (AAPT) diagnostic criteria (Arnold et al. 2018[15]) or the German Association of the Scientific Medical Societies (AWMF) diagnostic criteria[136].

4. Pharmacological or CBT interventions with quantitative self-report or objective measures of sleep as an outcome. Studies which did not measure sleep were excluded.
5. For pharmacological therapies the control intervention was required to be a placebo medication of the same appearance taken in the same regime.
6. For CBT studies, CBT had to be delivered by therapists trained in CBT or via the internet with an individual program based on the principles of CBT. All modalities of CBT were included as defined by a recent Health Technology Assessment[162]. Studies with combined interventions were excluded (e.g., physiotherapy with CBT).

2.2.2 Study quality and risk of bias

Three authors assessed the risk of bias using the Cochrane Risk of Bias tool[433], evaluating the following domains: random sequence generation; allocation concealment; blinding of study participants; blinding of study personnel; blinding of outcome assessors; incomplete outcome data addressed; selective reporting; and other potential bias. Each study was rated as low risk, some concerns, or high risk. Studies with missing baseline differences, adverse events, or incomplete data were considered high risk for reporting bias. The researchers independently evaluated all studies and resolved any discrepancies through discussion.

2.2.3 Data extraction

Data on participants, interventions, and results were extracted using Microsoft Forms. For studies with multiple interventions, data were recorded separately for each intervention group. Two researchers independently extracted the data for each study, resolving discrepancies through discussion. In the case of missing data, attempts were made to contact primary authors for further information.

2.2.4 Meta Analysis

A meta-analysis was conducted for interventions with sleep outcomes reported in more than three studies. Effect sizes were calculated as standardised mean differences (SMD), accounting for baseline differences between groups where possible. For parallel studies, the SMD was computed as the mean difference between the treatment and control groups, divided by the pooled standard deviation (SD). When available, baseline-adjusted change scores were used to determine SMD. The standard error (SE) for each SMD was computed based on the individual group SDs and sample sizes. As three of the four milnacipran studies reported mean differences at follow-up, these were converted into SMDs. For crossover studies, the pooled SD of differences was used, accounting for within-subject correlation (assumed at 0.5 if not otherwise reported). Studies with missing post-treatment outcome data were excluded, while missing variance data were imputed using baseline or the closest similar study. When studies included multiple treatment doses, the effects were pooled using inverse variance weighting, and subgroup analyses stratified by dosage

group were also performed. Subgroup analyses were also performed excluding studies with a crossover design. In cases where multiple sleep measurement methods were used (e.g. multiple self-report items or multiple physiological measures), validated tools (e.g. JSS, MOS-SS, PSQI) were preferentially chosen, and the most consistently used methods within the selected study group were extracted to improve comparison across the studies. Pooled effect sizes were interpreted as small (SMD 0.2), moderate (SMD 0.5), and large (SMD 0.8). Results were considered statistically significant if $p<0.05$.

A random-effects model was applied to account for variability between studies, with restricted maximum likelihood (REML) used to estimate tau-squared. The primary outcome measure was the pooled SMD with 95% confidence intervals (CIs). Heterogeneity was quantified using the I^2 statistic, with values >50% indicating substantial heterogeneity. Cochran's Q-test ($p < 0.1$) was used to assess statistical significance of heterogeneity. Prediction intervals were reported to estimate the range of potential effects in future studies[213].

Publication bias was assessed through visual inspection of funnel plots and Egger's regression test when ≥6 studies were available. Leave-one-out sensitivity analyses were conducted by removing each study in turn to evaluate the impact on the overall pooled effect. Influence analyses assessed the contribution of individual studies to heterogeneity and overall effect size.

All statistical analyses were conducted using R software (version 4.4.1). The `esc` package (version 0.5.1) was used to compute effect size and variance measures, the `meta` package (version 7.0-0) was used to conduct meta-analysis and create forest plots, and the `metafor` package (version 4.6-0) used to conduct leave-one-out and influence sensitivity analyses.

2.3 **Results**

2.3.1 Study selection

The initial search yielded 901 studies, with 322 duplicates excluded (**Figure 2-1**). After screening 579 titles and abstracts, 325 were removed, and the full texts of 254 articles were reviewed. Of these, 216 were assessed against inclusion criteria, resulting in 48 RCTs being included in the review[4; 16-18; 44; 62; 63; 71; 72; 76; 95; 111; 112; 129; 134; 169; 172-174; 178; 179; 189; 233; 256; 291; 300; 304; 305; 314; 319; 320; 338; 340; 342; 352; 358; 381; 383; 386; 388; 395; 397; 428; 458; 473; 498; 512; 513]. No additional studies were found through reference searches or grey literature.

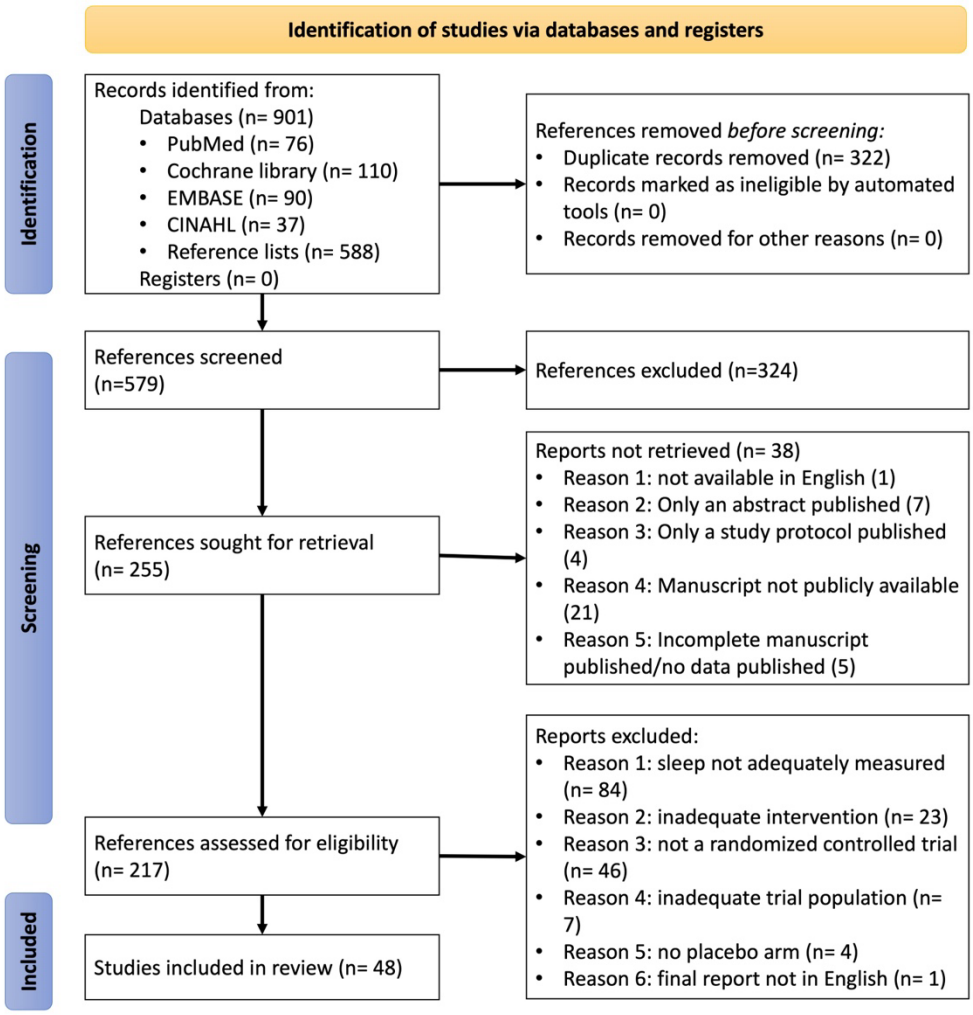


Figure 2-1. Flow diagram summarising literature search presented according to PRISMA guidelines

2.3.2 Study characteristics

This review included 11,140 (10,608 pharmacological; 532 CBT) participants with a mean (SD) age of 47.28 (4), of which 95.5% were female. Sample sizes varied widely, with a median (range) sample size of 125 (19-1,196) participants for the pharmacological studies, and 64 (26-148) for the CBT studies. The median (range) duration of treatment was 12 weeks (4-27) for pharmacological studies and 8 weeks (6-14) for CBT. Recruitment was reported from hospital outpatients, and the community; but the recruitment methodology was unclear in most studies.

Pharmacological therapies were evaluated in 40 studies[4; 16-18; 44; 62; 63; 71; 72; 95; 111; 112; 129; 169; 172-174; 178; 179; 189; 233; 304; 305; 319; 320; 338; 340; 342; 352; 358; 381; 383; 387; 388; 428; 458; 473; 498; 512; 513] **(Table 2-1)**, and CBT interventions were evaluated in 8 studies[76; 134; 256; 291; 300; 314; 395; 397] **(Table 2-2).**

2.3.3 Risk of bias

The risk of bias assessment found differences between pharmacological and CBT studies (**Figure 2-2)**. Among 40 pharmacological studies, ten (22.5%) were rated high risk[44; 72; 173; 174; 178; 189; 233; 338; 381; 458], 26 (66%) had some concerns[16; 17; 62; 63; 71; 95; 111; 112; 129; 169; 172; 178; 179; 304; 305; 320; 340; 342; 352; 358; 383; 387; 388; 428; 473; 498; 512; 513], and four (10%) were low risk[4; 18; 172; 319]. Pharmacological studies generally performed well in terms of randomisation and adherence to treatment protocols, with over half rated low risk in these areas. Missing data and outcome measurement also

showed reasonable levels of bias, with 24 (60%) studies low risk[4; 16-18; 111; 112; 129; 172; 173; 178; 179; 319; 340; 342; 358; 383; 387; 428; 473; 498; 513], though selective reporting remained a concern, with only 16 (41%) studies rated low risk in this domain[4; 17; 18; 62; 169; 172; 178; 304; 305; 319; 320; 359; 388; 426; 428; 513].

In contrast, CBT studies showed a higher overall risk of bias, with six (75%) rated high risk[76; 134; 256; 314; 395; 397] and none rated low risk (**Figure 2-2)**. Adherence to treatment protocols was poor, with five (62.5%) studies rated high risk for deviations from intended interventions[76; 256; 314; 395; 397]. Missing data and selective reporting were also problematic in CBT studies, possibly due to difficulties in maintaining participant engagement. Although randomisation was reasonably strong, with four (50%) CBT studies rated low risk[76; 291; 300; 314], issues in treatment adherence, missing data, and outcome measurement made achieving a low overall bias difficult.

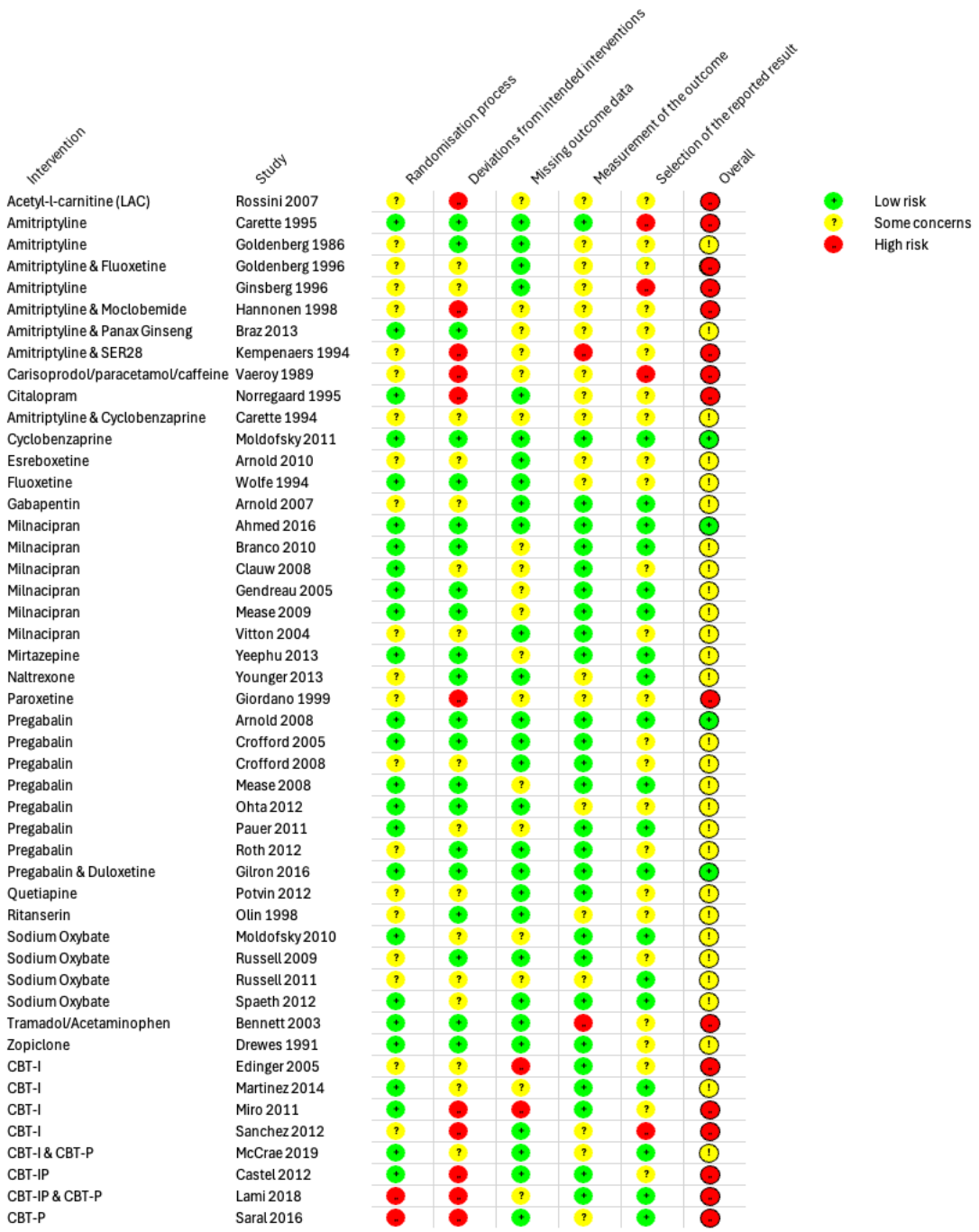


Figure 2-2. Risk of bias assessment for included studies.

The figure summarises the risk of bias across studies included in this systematic review, grouped by intervention type. Domains assessed include randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported result, and overall risk of bias. Green circles represent "low risk," yellow circles indicate "some concerns," and red circles denote "high risk" for each domain. The overall risk of bias for each study was determined by combining the judgments across all domains using the Cochrane Risk of Bias tool. Note some studies evaluated multiple interventions. CBT-I, Cognitive behavioural therapy for insomnia. CBT-P, Cognitive behavioural therapy for pain. CBT-IP, combined CBT-I and CBT-P.

2.3.4 **Pharmacological interventions** (Table 2-1)

2.3.4.1 Gabapentinoids

2.3.4.1.1 Pregabalin

Eight studies examined pregabalin in 3,834 patients using doses of 300mg, 450mg, and 600mg over 4 to 26 weeks[18; 111; 112; 172; 305; 340; 352; 383]. Gilron et al. [172] also evaluated pregabalin-duloxetine combination. A meta-analysis of pooled pregabalin doses showed a statistically significant moderate improvement on sleep quality (n=8, SMD -0.35, 95%CI -0.54 to -0.16) (**Figure 2-3A**). However, there was significant heterogeneity (t^2=0.04, p<0.01, $I^{2=}$78%), and the prediction interval suggests some uncertainty about future studies, although a beneficial effect is likely. Crofford et al. exerted the largest influence on the meta-analysis, but sensitivity analyses omitting this study did not meaningfully change the overall effect size[111]. Sensitivity analyses showed a trend towards a dose-response response, with better results at 450mg (SMD -0.43, 95%CI -0.71 to -0.16) than 300mg (SMD -0.26, 95%CI -0.46 to -0.07), but no improvement in efficacy at 600mg (SMD -0.29, 95%CI -0.72 to 0.14). There was no evidence of publication bias detected based on Egger's test (P=0.18).

2.3.4.1.2 Gabapentin

One study[17] investigated gabapentin doses of up to 1200mg daily over 12 weeks in 150 patients, and found a significant improvement in sleep quality of 22.6 points on the MOS-SS, compared to 8 points in the placebo group.

2.3.4.2 Antidepressants

2.3.4.2.1 Tricyclic antidepressants

Eight studies investigating amitriptyline in 541 patients, with doses ranging from 25mg to 50mg daily, and treatment duration 6 to 24 weeks[63; 71; 72; 173; 178; 179; 189; 233]. All measured sleep using a VAS, and five were included in a meta-analysis. There was a moderate improvement in sleep quality, but the confidence intervals were wide and the effect was not statistically significant (**Figure 2-3B,** n=6, SMD -0.71, 95%CI -2.05 to 0.63) (**Figure 2-3B**). There was substantial heterogeneity observed (t^2=1.22, p<0.01, I^2=82%) which may reflect the relatively small sample sizes and variable treatment durations examined. The wide prediction interval (-4.05 to 2.63) suggests considerable uncertainty. Of the two studies which evaluated PSG measures, one observed a 5.16% increase in time spent in stage 2 non-REM sleep with amitriptyline compared to placebo[72].

2.3.4.2.2 Selective serotonin reuptake inhibitors

Two studies investigated fluoxetine, of which one demonstrated a small improvement in sleep quality of 8.6 points on a 100-point VAS [178], which was more marked when

combined with amitriptyline (34.7 points), and one found no improvement[498]. A single study[338] investigated citalopram and did not find any improvement in sleep quality. Another study reported an improvement in sleep with paroxetine[174] although detailed results were not presented.

2.3.4.2.3 Serotonin-noradrenaline reuptake inhibitors

Six studies investigated milnacipran in 3,237 patients[4; 62; 95; 169; 304; 473]. None found a significant improvement in sleep except Vitton et al.[473] which reported improved patient's ability to stay asleep but did not report detailed outcome data. A meta-analysis of four studies showed no improvement in sleep quality (**Figure 2-3C,** n=4, SMD -0.01, 95%CI -0.07 to 0.05). There was low heterogeneity observed (t^2=0, p=0.82, I^2=0%), with a narrow prediction interval suggesting reasonable certainty about this finding.

A single study investigated esreboxetine in 268 patients[16]. Although there was no improvement on the MOS-SS overall sleep problems index, there was an improvement in somnolence, snoring, and quality of life MOS sub-scales.

One study evaluated duloxetine in 41 patients over 24 weeks and found no improvement in sleep quality[172]. The same study found that pregabalin-duloxetine combination did improve sleep quality on the MOS-SS sleep problems index compared to placebo but not compared to pregabalin alone.

2.3.4.2.4 Monoamine oxidase inhibitors

A single study investigated moclobemide in 98 patients and found no improvement in sleep quality on a VAS[189].

2.3.4.2.5 Atypical antidepressants

A single study of 40 patients[512] found that mirtazapine had no beneficial impact on sleep quality on the JSS compared with placebo.

2.3.4.3 Other agents

2.3.4.3.1 Sodium oxybate

Four studies investigated 4.5g and 6g sodium oxybate daily over 8 to 16 weeks in 1,516 patients[320; 386; 388; 428]. All measured sleep quality using the JSS. Meta-analysis of pooled doses demonstrated a significant moderate benefit on sleep quality (**Figure 2-3D,** n=4, SMD -0.72, 95%CI -1.26 to -0.18). There was significant heterogeneity observed (t^2=0.097, p<0.01, I^2=88%), with a wide prediction interval reflecting considerable uncertainty in the result. One study evaluated PSG and demonstrated increase time in NREM and decreased time in REM sleep in the sodium oxybate group compared to placebo[320].

2.3.4.3.2 Other pharmacological agents

One study of cyclobenzaprine demonstrated no improvement in sleep quality[71] however a smaller study of the same agent observed an increase in restorative sleep on PSG[319]. One study of 51 patients[358], found that quetiapine improved sleep quality on the PSQI. A small study of 45 patients found zopiclone improved self-reported sleep measures, but there were no differences in PSG measures[129].

No improvement in sleep quality was observed with naproxen[179], tramadol[44], panax ginseng[63], ritanserin[342], naltrexone[513], acetyl l-carnitine[381], carisoprodol with paracetamol and caffeine[458], and antidiencephalon immune serum[233].

Drug	Study	Setting	Randomised, N	Age, years	% Female	Groups (dose)	Treatment duration, weeks	Sleep measure(s)	Follow up, weeks	Completed study, %	Risk of Bias	Change from baseline	Overall result	Notes
Milnacipran	Ahmed, et al. 2016[4]	Single site in USA	19	median 49.2 (range, 28–72)	89.50%	100mg	12	MOS-SS Sleep Problem Index 2; PSG; Sleep Quality NRS (0-10)	14	15/19 (78.9%)	Low	MOS-SS Sleep Problems Index 2 (0-100); Milnacipran (-17.8); Placebo (-20.7) [NS]. Sleep Quality NRS (0-10): Milnacipran (+1.1); Placebo (+0.8) [NS]. PSG: WASO, mins: Milnacipran (-21); Placebo (-43.6) [NS]. TST, mins: Milnacipran (+21); Placebo (+45.4) [NS]. Sleep efficiency,%: Milnacipran (+4.8); Placebo (+11) [NS].	**No improvement in sleep quality with Milnacipran.**	Crossover trial, 6 weeks on each drug with 1 week washout
Gabapentin	Arnold, et al. 2007[17]	3 sites in USA	150	Gabapentin: mean 49.2 (SD 10.6); Placebo: 47.3 (11.8)	90%	up to 1200mg	12	MOS-SS	12	119/150 (79.3%)	Some concerns	MOS-SS Sleep Problems Index (0-100): Gabapentin (-22.6); Placebo (-8.0) [P=0.001]	**Improvement in sleep quality with gabapentin**	
Pregabalin	Arnold, et al. 2008[18]	84 centres in USA	750	mean 50.1 (11.4)	94.50%	300mg, 450mg, 600mg	14	MOS-SS; Sleep quality NRS (0-10)	14	600mg 60.1%, 450mg 66.8%, 300mg 67.2%, Placebo 67.9%	Low	MOS-SS SPI (0-100): 300mg (-11.39), 450mg (-12.85), 600mg (-15.09) vs placebo (-6.65). Sleep Quality NRS (0-10): 300mg (-1.75); 450mg (-2.03), 600mg (-2.05), Placebo (-1.04).	**Improvement in sleep quality with all pregabalin doses**	
Esreboxetine	Arnold, et al. 2010[16]	56 centres in USA	268	Esreboxetine: median 49.2 (21-79); Placebo 50.1 (20-84)	89.50%	2-8mg	8	MOS-SS	8	213/268 (79.8%)	Some concerns	MOS-SS Sleep Problems Index (0-100): Esreboxetine (-5.47); Placebo (-3.96) [NS]	**No improvement in sleep quality on MOS-SS SPI with Esreboxetine. However, improvement in somnolence, quantity of sleep, and snoring sub-scales**	
Tramadol/Acetaminophen	Bennett, et al. 2003[44]	Multicentre in USA	315	Mean 50 (10)	94%	37.5mg/325mg	13	Sleep Index 6; Sleep Index 9	13	313/315 (99.4%)	High	Sleep Index 6 (0-100): Tramadol (-8); Placebo (-8). Sleep Index 9 (0-100): Tramadol (-7); Placebo (-7). [NS]	**No improvement in sleep quality with tramadol/acetaminophen combination**	
Milnacipran	Branco, et al. 2010[62]	89 sites in 13 European countries	884	Placebo: mean 49.2 (10.3), Milnacipran: 48.3 (9.3)	Placebo 93.5%; milnacipran 95.1%	200mg	17	MOSS-SS Sleep Problems Index. Weekly sleep recall VAS (0-100)	16	678/884 (76.7%)	Some concerns	MOS-SS Sleep Problems Index 1 (0-100): Milnacipran -6.28; Placebo -6.73; Milnacipran vs Placebo: 0.45 (NS). MOS-SS Sleep Problems Index 2 (0-100): Milnacipran -6.93; Pregabalin -7.40; Milnacipran vs Placebo: 0.47 (NS). Weekly Sleep Recall VAS (0-100): Milnacipran -13.86; Placebo -9.59; Milnacipran vs Placebo -4.27 (P=0.007).	**Improvement in weekly sleep recall with Milnacipran, but no improvement in MOS-SS**	4 weeks dose escalation, 12 weeks stable dose, 9 weeks dose down-titration
Amitriptyline	Braz, et al. 2013[63]	Single site in Brazil	33	median 43.2 (range 27-58)	100%	25mg	12	Sleep Quality VAS 0-10	12	26/33 (78.8%)	Some concerns	Sleep Quality VAS (0-10): Amitriptyline (-3.8); Placebo (-4.9)	**No improvement in sleep quality with amitriptyline**	

Drug	Study	Setting	Randomised, N	Age, years	% Female	Groups (dose)	Treatment duration, weeks	Sleep measure(s)	Follow up, weeks	Completed study, %	Risk of Bias	Change from baseline	Overall result	Notes
Panax Ginseng	Braz, et al. 2013[63]	Single site in Brazil	36	median 43.2 (range 27-58)	100%	100mg	12	Sleep Quality VAS 0-10	12	25/36 (69.4%)	Some concerns	Sleep Quality VAS (0-10): P Ginseng (-3.8); Placebo (-4.9) [NS between groups]	**No improvement in sleep quality with Panax Ginseng**	
Amitriptyline	Carette, et al. 1994[71]	11 sites in Canada	126	Amitriptyline mean 44.1; Placebo 47.1	92.90%	10-50mg	24	Sleep quality VAS 0-100	24	98/126 (77.7%)	Some concerns	Detailed results not given	**No improvement in sleep quality with Amitriptyline**	
Cyclobenzaprine	Carette, et al. 1994[71]	11 sites in Canada	124	CBP: mean 43.4; Placebo 47.1	94.40%	10-30mg	24	Sleep quality VAS 0-100	24	86/124 (69.4%)	Some concerns	Detailed results not given	**No improvement in sleep quality with Cyclobenzaprine**	
Amitriptyline	Carette, et al. 1995[72]	Single site in Canada	22	mean 43.8 (8.0)	95.50%	25mg	8	Sleep quality VAS (0-10); PSG	8	20/22 (90.9%)	High	Sleep quality VAS (0-10): Amitriptyline (-3.96); Placebo (-0.98) [P<0.05]. PSG: TST, hours: AMI (+0.42); Placebo (+0.14). Stage 1,%: AMI (+0.69); Placebo (-1.9). Stage 2,%: AMI (+5.16); Placebo (+0.94). Stage 3,%: AMI (-0.58); Placebo (+0.45). Stage 4,%: AMI (-2.6); Placebo (+0.09). Latency sleep, minutes: AMI (-2.76); Placebo (-10.04). Latency stage 3, minutes: AMI (-2.76); Placebo (-10.04). Latency stage 4, minutes: AMI (+1.41); Placebo (+0.2). Latency REM, minutes: AMI (+2.85); Placebo (-5.68). Stage 2 alpha, rating: AMI (+0.15); Placebo (-0.12). Stage 3 alpha, rating: AMI (-0.03); Placebo (+0.12). Stage 4 alpha, rating: AMI (+0.05); Placebo (+0.23). Stage 3 or 4 alpha, rating: AMI (+0.05); Placebo (+0.08).	**No improvement in sleep quality with amitriptyline. On PSG, increase in Stage 2 NREM sleep and decreased sleep latency in amitriptyline.**	Crossover trial
Milnacipran	Clauw, et al. 2008[95]	86 centres in USA	1196	Placebo: mean 50.7 (10.4); 100mg 49.5 (10.9); 200mg 50.4 (10.6)	96.20%	100mg, 200mg	15	MOS-SS Sleep Problems Index 2	15	811/1196 (67.8%)	Some concerns	MOS-SS Sleep Problems Index 2 (0-100): Milnacipran 100mg +1.7; Milnacipran 200mg +2.3; Placebo +3.0 (all NS).	**No improvement in sleep quality with Milnacipran**	6-month extension study
Pregabalin	Crofford, et al. 2005[112]	40 centres in USA	530	450mg: mean 48.9 (11.3); 300mg: 47.7 (10.1); 150mg: (10.4); Placebo: 49.7 (10.7)	91.30%	150mg, 300mg 450mg	8	MOS-SS; Sleep quality NRS (0-10)	8	410/530 (77.3%); Placebo 74%; 150mg 78%; 300mg 82.8%; 450mg 75%	Some concerns	MOS-SS Sleep Problems Index (0-100): 150mg (-16.84); 300mg (-17.24), 450mg (-22.06), Placebo (-8.34). Sleep quality NRS (0-10): 150mg (-1.69); 300mg (-1.92), 450mg (-2.61), Placebo (-1.3).	**Improvement in sleep quality with all pregabalin doses**	
Pregabalin	Crofford, et al. 2008[111]	95 sites in USA	566	Placebo: mean 49.6 (10.5); Pregabalin: 48.8 (11.9)	90.10%	300mg, 450mg and 600mg	26	MOS-SS Sleep Problems Index	26	162/566 (28.6%)	Some concerns	MOS-SS Sleep Problems Index (0-100): 300mg (-40.2); 450mg (-42.5), 600mg (-39), Placebo (-40.4). Sleep quality NRS (0-10): 300mg (-1.69); 450mg (-1.92), 600mg (-2.61), Placebo (-1.3).	**No significant improvement in sleep quality with all pregabalin doses**	

Drug	Study	Setting	Randomised, N	Age, years	% Female	Groups (dose)	Treatment duration, weeks	Sleep measure(s)	Follow up, weeks	Completed study, %	Risk of Bias	Change from baseline	Overall result	Notes
Zopiclone	Drewes, et al. 1991[129]	Single site in Denmark	45	Mean 50	100%	7.5mg	12	PSG; Leeds Sleep Evaluation Questionnaire (VAS); Spiegel Sleep Questionnaire	12	41/45 (91.1%)	Some concerns	LSEQ: Sleep onset latency (0-100): Zopiclone (+15.3); placebo (+3.8) [P<0.05]. Quality of sleep (0-100): Zopiclone (+14.5); Placebo (+1.7) [P<0.05]. Pattern of awakening: Zopiclone (+2.9); placebo (+0.2) [NS]. Feeling on waking: Zopiclone (-3.2); placebo (-6.3) [NS]. Feeling now: Zopiclone (-4.5); Placebo (-6.0) [NS]. Balance and coordination: Zopiclone (+1.9); placebo (-0.4) [NS]. Spiegel Sleep Questionnaire (1-5): Sleep onset latency: Zopiclone (-0.9); placebo (-0.2) [P<0.05]. Quality of sleep: Zopiclone (-1.0); placebo (-0.6) [P<0.05]. Duration of sleep: Zopiclone (-0.9); placebo (+0.2) [P<0.05]. Awakenings at night: Zopiclone (-0.8); placebo (-0.2) [P<0.05]. Dreams: Zopiclone (0.5); placebo (-0.1) [NS]. Condition in the morning: Zopiclone (-0.7); Placebo (-0.4) [P<0.05]. PSG: NREM Stage 1,%: Zopiclone (-2.1); Placebo (-1.5); NREM Stage 2,%: Zopiclone (+11.9); Placebo (+9.0); NREM Stage 3&4,%: Zopiclone (-5.3); Placebo (-5.7). REM,%: Zopiclone (-2.9); Placebo (+5.1). Number of awakenings: Zopiclone (-24); Placebo (-4). Number of stage shifts: Zopiclone (-12); Placebo (-7). [all PSG NS]	**Improvement in self-reported sleep quality, but no differences in PSG findings, in Zopiclone**	
Milnacipran	Gendreau, et al. 2005[473]	14 sites in USA	125	Mean 47.0 (11.1)	98%	200mg	13	JSS	12	90/125 (72%)	Some concerns	No significant change in JSS. Detailed results not reported.	**No improvement in sleep quality with Milnacipran**	
Duloxetine	Gilron, et al. 2016[172]	Single centre in Canada	41	Median: 56 (20-71)	88%	Up to 120mg	24	MOS-SS	24	33/41 (80.4%)	Low	MOS-SS SPI-1: Duloxetine (-1.0), Placebo (+1.8) MOS-SS SPI-2: Duloxetine (-1.0), Placebo (+0.5)	**Improvement in MOS-SS Sleep Problem Indices 1&2 Pregabalin/Duloxetine combination**	Crossover trial. 4 periods of 6 weeks on each drug
Pregabalin	Gilron, et al. 2016[172]	Single centre in Canada	41	Median: 56 (20-71)	88%	Up to 450mg	24	MOS-SS	24	33/41 (80.4%)	Low	MOS-SS SPI-1: Pregabalin (-11.9), Placebo (+1.8) MOS-SS SPI-2: Pregabalin (-13.1), Placebo (+0.5)	**Improvement in MOS-SS Sleep Problem Indices 1&2 with Pregabalin and Pregabalin/Duloxetine combination**	Crossover trial. 4 periods of 6 weeks on each drug
Pregabalin/Duloxetine	Gilron, et al. 2016[172]	Single centre in Canada	41	Median: 56 (20-71)	88%	450mg/ 120mg	24	MOS-SS	24	33/41 (80.4%)	Low	MOS-SS SPI-1: Pregabalin-Duloxetine (-15.0), Placebo (+1.8) MOS-SS SPI-2: Pregabalin-Duloxetine (-15.8), placebo (+0.5)	**Improvement in MOS-SS Sleep Problem Indices 1&2 with Pregabalin/Duloxetine combination**	Crossover trial. 4 periods of 6 weeks on each drug

Drug	Study	Setting	Randomised, N	Age, years	% Female	Groups (dose)	Treatment duration, weeks	Sleep measure(s)	Follow up, weeks	Completed study, %	Risk of Bias	Change from baseline	Overall result	Notes
Paroxetine	Giordano, et al. 1999[174]	Single site in Italy	40	Mean: 31 (7.2)	100%	20mg	12	Sleep Quality VAS 0-10	12	29/40 (72.5%)	High	Values of VAS not indicated	**Improvement in sleep quality with paroxetine, but values not provided**	
Amitriptyline	Goldenberg, et al. 1986[179]	Single site in USA	62	Median: 43.8 (21-69)	95.20%	25mg	6	Sleep quality VAS 0-10	6	58/62 (93.5%)	Some concerns	Sleep Quality VAS (0-10): Amitriptyline (-3.2); Amitriptyline + Naproxen (-2.0).	**Improvement in sleep quality with amitriptyline**	
Amitriptyline	Goldenberg, et al. 1996[178]	Single site in USA	31	Mean: 43.2 (9.1)	90.30%	25mg	6	Sleep quality VAS 0-100	6	19/31	Some concerns	Sleep Quality VAS (0-100): Amitriptyline (-15.2); Amitriptyline + Fluoxetine (-34.7). Overall amitriptyline effect, P<0.001)	**Improvement in sleep quality with amitriptyline. More marked with fluoxetine combination.**	Cross-over trial
Amitriptyline	Ginsberg, et al. 1996[173]	Single site in France	51	Mean: 46 (12)	83%	25mg	8	Sleep quality VAS (0-10)	8	46/51 (90.2%)	High	Sleep Quality VAS (0-10): Amitriptyline (-2.6); Placebo (-0.3)	**Improvement in sleep quality with amitriptyline**	
Fluoxetine	Goldenberg, et al. 1996[178]	Single site in USA	31	Mean: 43.2 (9.1)	90.30%	20mg	6	Sleep quality VAS 0-100	6	19/31	Some concerns	Sleep Quality VAS (0-100): Fluoxetine (-8.6); Amitriptyline + Fluoxetine (-34.7). (Overall Fluoxetine effect, P=0.04)	**Improvement in sleep quality with fluoxetine**	Cross-over trial
Amitriptyline	Hannonen, et al. 1998[189]	Single site in Finland	97	Amitriptyline, mean: 49.7 (8.2); Placebo: 48.9 (8.9)	100%	25 to 37.5mg	12	Sleep quality VAS 0-10	12	62/97 (63.9%)	High	Sleep Quality VAS (0-10): Amitriptyline -2.3; placebo -0.7.	**Improvement in sleep quality with amitriptyline**	
Moclobemide	Hannonen, et al. 1998[189]	Single site in Finland	98	Moclobemide 47.6 (8.7); Placebo 48.9 (8.9)	100%	450 to 600mg	12	Sleep quality VAS 0-10	12	60/98 (61.2%)	High	Sleep Quality VAS (0-10): Moclobemide -0.0; placebo -0.7.	**No improvement in sleep quality with Moclobemide**	
Amitriptyline	Kempenaers, et al. 1994[233]	Single site in Belgium	24	Mean: 38 (7)	100%	50mg	8	Sleep Quality VAS (0-100). PSG	8	14/24 (58.3%)	High	Sleep Quality VAS (0-100): AMI (+17); Placebo (+2). PSG: TST, mins: AMI (-22); Placebo (+40) [NS]. Sleep onset latency, mins: AMI (+6); Placebo (-3) [NS]. Sleep efficiency,%: AMI (-6.7); Placebo (+2) [NS]. Arousal index, n/h: AMI (+3); Placebo (+2) [P=0.029]. Stage shifts index, n/h: AMI (+5); Placebo (-3) [NS]. Stage 1, mins: AMI (+10); Placebo (+4) [NS]. Stage 2, mins: AMI (-3); Placebo (+37) [NS]. Stage 3, mins: AMI (-14); Placebo (+1) [NS]. Stage 4, mins: AMI (-17); Placebo (-4) [NS]. REM sleep, mins: AMI (+1); Placebo (-1) [NS]. REM latency, mins: AMI (+9); Placebo (-3) [NS].	**No improvement in sleep quality or PSG parameters for amitriptyline**	

Drug	Study	Setting	Randomised, N	Age, years	% Female	Groups (dose)	Treatment duration, weeks	Sleep measure(s)	Follow up, weeks	Completed study, %	Risk of Bias	Change from baseline	Overall result	Notes
Antidiencephalon Immunoglobulin (SER282)	Kempenaers, et al. 1994[233]	Single site in Belgium	24	Mean: 38 (7)	100%	20 mg/ml	8	Sleep Quality VAS (0-100). PSG	8	17/24 (70.8%)	High	Sleep Quality VAS (0-100): SER282 (-27); Placebo (+2). PSG: TST, mins: SER282 (+6); Placebo (+40) [NS]. Sleep onset latency, mins: SER282 (-3); Placebo (-3) [NS]. Sleep efficiency,%: SER282 (+5.2); Placebo (+2) [NS]. Arousal index, n/h: SER282 (+0); Placebo (+2) [P=0.029]. Stage shifts index, n/h: SER282 (+2); Placebo (-3) [NS]. Stage 1, mins: SER282 (+6); Placebo (+4) [NS]. Stage 2, mins: SER282 (+2); Placebo (+37) [NS]. Stage 3, mins: SER282 (-4); Placebo (+1) [NS]. Stage 4, mins: SER282 (+13); Placebo (-4) [NS]. REM sleep, mins: SER282 (-10); Placebo (-1) [NS]. REM latency, mins: SER282 (-38); Placebo (-3) [NS].	**No improvement in sleep quality or PSG parameters for SER282**	
Pregabalin	Mease, et al. 2008[426]	79 sites in USA	751	600mg, mean: 48.7 (11.2); 450mg: 47.7 (10.8); 300mg: 50.1 (10.4); placebo 48.6 (11.3)	94.40%	300mg, 450mg, 600mg	13	MOS-SS; Sleep quality NRS (0-10)	14	485/751 (64.8%)	Some concerns	MOS-SS Sleep Problems Index (0-100): 300mg (-19.1); 450mg (-20.41); 600mg (-19.49); Placebo (-14.29). Sleep Quality NRS (0-10): 300mg (-2.19); 450mg (-2.29); 600mg (-2.53); placebo (-1.32)	**Improvement in sleep quality with pregabalin**	
Milnacipran	Mease, et al. 2009[304]	59 sites in USA	888	Placebo, mean: 49.4 (10.1); 100mg: 49.9 (10.6); 200mg: 49.2 (11)	95.60%	100mg, 200mg	27	MOS-SS	27	512/888 (57.7%)	Some concerns	MOS-SS Sleep Problems Index 1 (0-100): Milnacipran 100mg +0.12; Milnacipran 200mg -1.65; Placebo -0.06 (all NS). MOS-SS Sleep Problems Index 2 (0-100): Milnacipran 100mg -0.43; Milnacipran 200mg -2.11; Placebo -0.96 (all NS).	**No improvement in sleep quality with Milnacipran**	3 weeks dose escalation, 24 weeks stable dose
Sodium Oxybate	Moldofsky, et al. 2010[320]	21 sites in USA	195	Mean: 46.5 (11.3)	93.80%	4.5g, 6g	8	JSS; PSG	8	151/195 (77.4%)	Some concerns	JSS (0-20): SXB 4.5.g (-7.1), 6g (-8.4); placebo (-3.8). PSG WASO (mins): 4.5g (4.2); 6g (-39.7); placebo (16.2). PSG TST (mins): 4.5g (-11.4); 6g (39.4); Placebo (10.1). PSG sleep onset latency (mins): 4.5g (3.2); 6g (-5.9); placebo (0.9). PSG sleep efficiency (%): 4.5g (-2.4); 6g (8.9); placebo (3.0). PSG REM sleep (mins): 4.5g (-23.8); 6g (-18.6). PSG NREM sleep (mins): 4.5g (12.4); 6g (57.9); placebo (12.4).	**Improvement on subjective sleep quality with both doses of sodium oxybate. Increased NREM and decreased REM sleep with sodium oxybate.**	
Cyclobenzaprine	Moldofsky, et al. 2011[319]	2 sites in Canada	36	CBP, mean: 45.9 (11.4); Placebo: 39.3 (9.3)	97%	up to 4mg	8	PSG	8	36/36 (100%)	Low	TST, hours: CBP (+0.7); Placebo (-0.1) [NS]. Sleep efficiency,%: CBP (+11.5); Placebo (+3.0) [NS]. REM,%: CBP (-2.9); Placebo (+1.0) [P=0.007]. Stage 1,%: CBP (+1.2); Placebo (-0.4) [NS]. Stage 2,%: CBP (+3.5); Placebo (-2.6) [P=0.021]. Stage 3,%: CBP (+1.2); Placebo (-0.2) [NS]. Stage 4,%: CBP (-3.0); Placebo (+2.5) [P=0.029].	**Improvement in restorative sleep, increase in Stage 2 & decrease in Stage 4 & REM Sleep with cyclobenzaprine**	

Drug	Study	Setting	Randomised, N	Age, years	% Female	Groups (dose)	Treatment duration, weeks	Sleep measure(s)	Follow up, weeks	Completed study, %	Risk of Bias	Change from baseline	Overall result	Notes
Citalopram	Nørregaard, et al. 1995[338]	Single site in Denmark	42	Citalopram, mean: 48 (9); Placebo: 50 (9)	Not given	20mg to 40mg	8	Sleep Quality NRS (0-10) on FIQ	8	33/42 (78.6%)	High	FIQ, Sleep Quality NRS (0-10): Citalopram (+1.0); Placebo (+0.1) [NS]	**No improvement in sleep quality with citalopram**	
Pregabalin	Ohta, et al. 2012[340]	44 sites in Japan	501	Pregabalin, mean: 47.9 (12); Placebo: 46.7 (12.6)	88.90%	150mg to 450mg	15	MOS-SS; NRS 0-10 (secondary outcomes)	15	415/501 (82.8%)	Some concerns	MOS-SS Sleep Problems Index (0-100): Pregabalin (-10.3); Placebo (-6.14). Sleep Quality NRS (0-10): Pregabalin (-1.52); Placebo (-0.79)	**Improvement in sleep quality with pregabalin**	
Ritanserin	Olin, et al. 1998[66]	Single site in Sweden	54	Median: 44 (24-59)	100%	10mg	16	Sleep quality VAS (0-10)	16	51/54 (94.4%)	Some concerns	No detailed results given	**No improvement in sleep quality with ritanserin**	
Pregabalin	Pauer, et al. 2011[352]	73 sites internationally	736	Mean: 48.5 (11.2)	91.00%	300mg, 450mg, 600mg	14	MOS-SS; NRS 0-10 (secondary outcomes)	14	518/738 (70.2%)	Some concerns	MOS-SS Sleep Problems Index (0-100): 300mg (-13.18); 450mg (-19.26); 600mg (-18.7; placebo (-5.99). Sleep Quality NRS (0-10): 300mg (-1.45); 450mg (-1.72); 600mg (-1.95); placebo (-0.94)	**Improvement in sleep quality with all pregabalin dose**	*Denmark, 2 centres, France 5, Germany 5, Italy 6, Portugal 4, Spain 4, Sweden 4, Switzerland 3, The Netherlands 5, UK 5, Australia 4, Canada 12, India 4, Korea 3, Mexico 4, Venezuela 3*
Quetiapine	Potvin, et al. 2012[358]	Single site in Canada	51	Quetiapine, mean: 50.0 (11.7); Placebo: 49.1 (8.7)	100%	50 to 300mg	12	PSQI	12	43/51 (84.3%)	Some concerns	PSQI (0-21): Quetiapine (-3.5); Placebo (0) [P=0.009].	**Improvement in sleep quality with Quetiapine XR**	
Acetyl-l-carnitine (LAC)	Rossini, et al. 2007[381]	7 sites in Italy	102	LAC, mean: 47.3 (11.7). Placebo: 46.3 (10.4)	97%	1 dose IM 1g	8	Sleep quality VAS (1-100)	12	75/102 (73.5%)	High	Values of VAS not provided	**No improvement in sleep quality with LAC**	
Pregabalin	Roth, et al. 2012[383]	19 sites in USA, Germany & Canada	119	Median 48.4 (range 27-77)	86.60%	300mg to 450mg	4	Sleep Quality NRS (0-10); Sleep diary; PSG	4	103/119 (85.7%)	Some concerns	Sleep Quality NRS (0-10): Pregabalin vs Placebo: +0.89. PSG: WASO, mins: Pregabalin (-56.8); placebo (-37.6). TST, mins: Pregabalin (+72); Placebo (+50). Sleep efficiency,%: Pregabalin (+15.8); Placebo (+10.4). Latency to persistent sleep: Pregabalin (-24.6); Placebo (-17.5). Slow wave sleep,%: Pregabalin (+1.9); Placebo (-0.3).	**Improvement in sleep quality with pregabalin**	Crossover trial; 2 weeks on each drug

Drug	Study	Setting	Randomised, N	Age, years	% Female	Groups (dose)	Treatment duration, weeks	Sleep measure(s)	Follow up, weeks	Completed study, %	Risk of Bias	Change from baseline	Overall result	Notes
Sodium Oxybate	Russell, et al. 2009[387]	21 sites in the United States	195	Placebo, mean: 47.3 (10.6); 4.5g: 47.4 (12.1); 6g: 45.5 (11.6)	94.60%	4.5g, 6g	8	JSS	8	147/195	Some concerns	JSS (0-20): SXB 4.5.g (-5.5), 6g (-6.0); placebo (-1.0).	**Significant improvement in sleep quality with both doses of sodium oxybate**	
Sodium Oxybate	Russell, et al. 2011[388]	74 clinical sites in USA	548	Mean: 47.0 (11.3)	91.20%	4.5g, 6g	14	JSS	16	334/548 (60.9%)	Some concerns	JSS (0-20): SXB 4.5.g (-6.1), 6g (-6.2); placebo (-2.9).	**Improvement in sleep quality with both doses of sodium oxybate**	
Sodium Oxybate	Spaeth, et al. 2012[428]	108 centres internationally	578	Mean: 46.6 (10.7)	89.50%	4.5g, 6g	14	JSS	14	376/573 (65.6%)	Some concerns	JSS (0-20): Sodium Oxybate 4.5g (-4.0); 6g (-5.0); Placebo (-1.0). (all significant vs placebo)	**Improvement in sleep quality with both doses of sodium oxybate**	France, Germany, Italy, Netherlands, Spain, UK, USA
Carisoprodol/paracetamol/caffeine	Vaerøy, et al. 1989[458]	Single site in Norway	58	Mean: 47.7 (13.7)	100%	1200mg/1920mg/384mg	8	Sleep quality VAS (0-10)	8	43/58 (74.1%)	High	Sleep Quality VAS (0-10): treatment (+3.3); placebo (+2.7). [NS]	**No improvement in sleep quality with treatment**	
Milnacipran	Vitton, et al. 2004[473]	14 sites in USA	125	46.2 to 48.0 (group values not given)	96% to 98%	≤200mg, 400mg	12	JSS	12	90/125 (72%)	Some concerns	JSS (0-20): Milnacipran 200mg (-1.3); 400mg (-1.3); Placebo (-0.5). [NS]	**No improvement in sleep quality with milnacipran**	
Fluoxetine	Wolfe, et al. 1994[498]	Single site in USA	42	Fluoxetine, mean: 48 (10.1); Placebo: 52.9 (11.3)	100%	20mg	6	Sleep Quality VAS (0-15)	6	24/42 (58.5%)	Some concerns	Sleep Quality VAS (0-15): Fluoxetine (-2.0); Placebo (-2.0) [NS]	**No improvement in sleep quality with Fluoxetine**	
Mirtazapine	Yeephu, et al. 2013[512]	Single site in Thailand	40	Mean: 44.7 (10.8)	100%	15mg, 30mg	13	JSS	13	32/40 (80%)	Some concerns	JSS (0-20): Mirtazapine 15mg (-5.92); 30mg (-6.54); Placebo (-2.8). [NS]	**No improvement in sleep quality with mirtazapine**	
Naltrexone	Younger, et al. 2013[513]	USA	31	Mean: 42.7 (12.9)	100%	4.5mg	12	Sleep quality VAS 0-100	12	28/31 (90.3%)	Some concerns	Sleep quality VAS (0-100),% improvement: Naltrexone (+10.4); Placebo (+9.2) [NS]	**No improvement in sleep quality with naltrexone**	Crossover study

Table 2-1. Characteristics and Outcomes of Included Pharmacological Studies for Sleep Quality in Patients with Fibromyalgia.

This table summarises the characteristics, interventions, sleep outcome measures, and key findings of pharmacological studies investigating sleep quality in fibromyalgia. Information includes study settings, sample sizes, participant demographics, treatment dosages and durations, sleep measurement tools, follow-up periods, completion rates, risk of bias, and reported changes in sleep outcomes. Results are presented with statistical significance where available, highlighting both subjective (e.g., sleep scales) and objective (e.g., polysomnography) measures of sleep quality. The findings highlight variable effects of pharmacological interventions on sleep quality, with some studies showing significant improvements and others reporting no notable differences. Methodological details, such as crossover designs and specific biases, are noted where relevant. Abbreviations: NI (Not Indicated), MOS-SS (Medical Outcomes Study Sleep Scale), NRS (Numerical Rating Scale), PSG (Polysomnography), JSS (Jenkins Sleep Scale), PSQI (Pittsburgh Sleep Quality Index), VAS (Visual Analogue Scale), FIQ (Fibromyalgia Impact Questionnaire), EEG (Electroencephalogram), WASO (Wake After Sleep Onset), TST (Total Sleep Time), NS (Not Significant), and mg (milligrams).

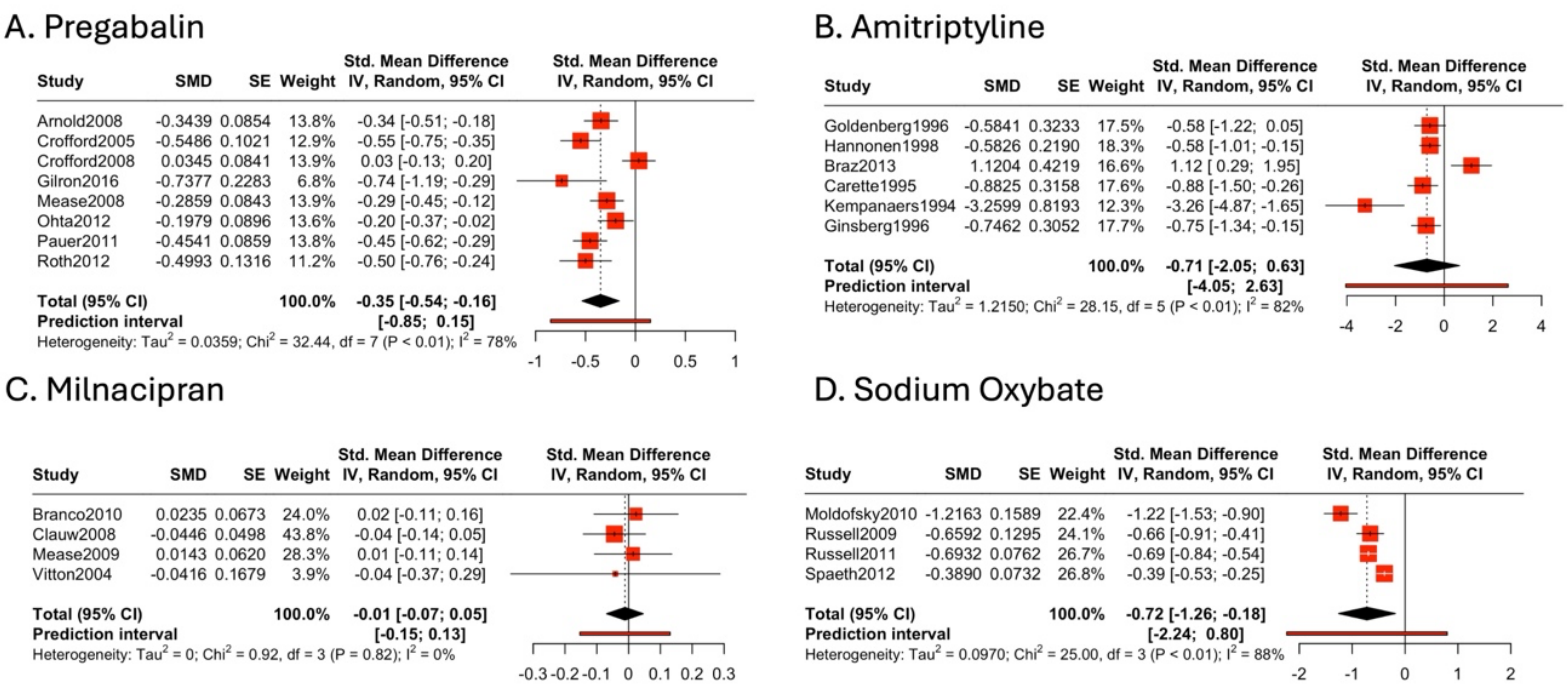


Figure 2-3. Forest plot of the effect of pharmacological interventions on sleep quality in fibromyalgia.

The diamond at the bottom depicts the overall pooled effect, with its width representing the 95% confidence interval (CI). The size of each square corresponds to the weight of the study in the meta-analysis. For pregabalin (A), the pooled standardised mean differences (SMDs) and variances were calculated across all doses evaluated in each study, with crossover studies (e.g., Gilron et al. 2016, Roth et al. 2012) appropriately handled using variance reduction techniques. Amitriptyline (B) utilised baseline-adjusted standardised mean difference (SMD) to account for pre-treatment differences between intervention and control groups. For sodium oxybate (C), SMDs for 4.5g and 6g doses were combined using inverse variance weighting to produce a pooled effect. Milnacipran (D) SMDs were calculated based on the change scores from baseline to follow-up and pooled for studies with multiple doses. Hartung-Knapp adjustment (HK) was applied in all random-effects models to provide more accurate estimation of uncertainty.

2.3.5 Cognitive Behavioural Therapy (Table 2-2)

2.3.5.1 CBT-I

Seven studies investigated CBT-I in 387 patients; five evaluated CBT-I alone (n=239)[134; 291; 300; 314; 395], while two studied CBT-I as part of a combined CBT-I/CBT-P program (n=148)[76; 256]. All CBT programmes were delivered by a clinician and lasted 6 to 14 weeks. A range of outcome measures were evaluated in relation to sleep, including the PSQI (n=3), MOS-SS (n=1), insomnia symptom questionnaire (n=1), sleep quality Likert scale (n=1), and PSG (n=3). In contrast to the pharmacological studies evaluated, the majority of CBT intervention studies considered sleep-related outcome measures as primary outcomes. Three studies employed sleep hygiene as a control, while four used treatment as usual.

A meta-analysis of CBT-I showed a statistically significant moderate improvement on sleep quality (n=7, SMD -0.63, 95%CI -0.98 to -0.27) (**Figure 2-4A**). There was moderate heterogeneity observed (t^2=0.06, p=0.15, I^2=37%), with a relatively narrow prediction interval suggesting reasonable certainty regarding this finding. Sensitivity analyses show that Castel et al.[76] had the largest influence, but omitting this study did not affect the overall effect size. There was no evidence of publication bias on Egger's test (P=0.60).
Of the studies which evaluated PSG, Edinger et al. observed an improvement in sleep onset latency (SOL)[134], while McCrae et al. observed lower wake-after-sleep-onset (WASO)[300], and Sanchez et al. found an increase in time spent in deep sleep[395]. Three

studies continued follow-up beyond the treatment period, and two[76; 300] demonstrated that improvement in self-rated sleep quality was maintained after 6 months, while the other study[291] found that the beneficial effect had subsided at this time.

2.3.5.1.1 Effects of CBT-I on cognitive performance

One included trial, by Miró et al, evaluated cognitive performance using the Attentional Network Test-Interactions (ANT-I) in 44 women with fibromyalgia and comorbid insomnia (N=22 per group)[314]. No improvements were observed in any attentional indices in the control (sleep hygiene) group following treatment. In contrast, participants who received CBT-I showed moderate-to-large improvements in the alertness (d=0.70, P=0.047) and executive function (d=0.82, P=0.018) indices, but not the orienting index (P=0.43, effect size not reported). Improvement in executive function was moderately correlated with better sleep quality on the PSQI (r=0.4, P=0.026), suggesting a link between sleep improvement and cognitive performance. No associations were found with changes in fibromyalgia-related quality of life (FIQ). However, tests of between-group effects were not reported, leaving it uncertain whether the observed effects differed across treatment groups.

2.3.5.2 CBT-P

Four studies evaluated CBT targeting pain in 288 patients[76; 256; 300; 397], with treatment duration ranging from 2 days to 26 weeks. Sleep outcome measures included

PSQI (n=1), MOS-SS (n=1), sleep quality VAS or Likert scale (n=2), and PSG (n=1). All studies used treatment as usual or waiting list control. In contrast to CBT-I, meta-analysis showed no improvement in sleep with CBT-P (**Figure 2-4B,** SMD -0.61, 95%CI -1.70 to 0.48). There was substantial heterogeneity observed (t^2=0.39, p<0.01, I^2=83%), and a wide prediction interval suggesting considerable uncertainty.

Intervention	Study	Setting	Randomised, N	Age, years	% Female	Control	Treatment duration	Sleep measure(s)	Follow-up, weeks	Completed study, %	Risk of bias	Change from baseline at post-treatment follow-up	Overall result
CBT-I	Edinger, et al. 2005[134]	Single site in USA	29	48.6 (8.2)	96.6%	TAU	1 session/week for 6 weeks. First session 45-60mins, subsequent session 15-30 mins.	Insomnia Symptom Questionnaire; Sleep diary; actigraphy; PSG	8	82.80%	High	**ISQ (0-100): CBT-I (-13.0); TAU (-0.4) [P<0.05].** Sleep diary: **Sleep efficiency,%: CBT-I (+7.4); TAU (+2.1). TWT, min: CBT-I (-43.3); TAU (-9.5).** TST, min: CBT-I (+11.4); TAU (+6.5). **SOL, min: CBT-I (-16.0); TAU (-2.7).** WASO, min: CBT-I (-32.8); TAU (-13.8). Actigraphy: Sleep efficiency,%: CBT-I (+2.3); TAU (-0.2). TWT, min: CBT-I (-16.2); TAU (-2.3). TST, min: CBT-I (-10.8); TAU (-2.7). **SOL, min: CBT-I (-5.5); TAU (-2.7). WASO,** min: CBT-I (-9.7); TAU (-6.9).	**Improvement in sleep quality with CBT-I. Improvement in self-reported sleep efficiency, TWT, SOL. Improvement in SOL on actigraphy.**
CBT-I	Martínez, et al. 2014[291]	Single site in Spain	64	47.6 (6.8)	100%	SH	90 mins/week for 6 weeks	PSQI	6	89%	Some concerns	**PSQI (0-21): CBT-I (-3.97); SH (-1.45)[P<0.05]**	**Improvement in sleep quality with CBT-I. Not maintained after 6 months**
CBT-I	McCrae, et al. 2019[300]	Single site in USA	76	CBT-I: 54.13 (11.03); WLC: 52.27 (11.19)	100%	WLC	50 mins/week for 8 weeks	Sleep quality Likert scale (1-5); sleep diary; actigraphy; PSG	8	72.40%	Some concerns	**Sleep quality (1-5): CBT-I (+0.7); WLC (+0.19) [P<0.05].** Sleep diary: SOL, min: CBT-I (-36.05); WLC (-20.16) [NS]. **WASO, min: CBT-I (-29.94); WLC (-10.45) [P<0.05].** TST, min: CBT-I (+29.83); WLC (+32.52) [NS]. **Sleep efficiency,%: CBT-I (+15.12); WLC (+6.49) [P<0.05].** PSG: SOL, min: CBT-I (-10.3); WLC (+1.38). **WASO, min: CBT-I (-19.35); WLC (+1.38).** TST, min: CBT-I (-10.98); WLC (-16.54). Sleep efficiency,%: CBT-I (+5.25); WLC (+1.25). Actigraphy: SOL, min: CBT-I (-13.98); WLC (-11.86). WASO, min: CBT-I (-6.76); WLC (-0.99). TST, min: CBT-I (-16.38); WLC (-8.43). Sleep efficiency,%: CBT-I (+2.4); WLC (+1.21).	**Improvement in sleep quality with CBT-I. Improvement maintained after 6 months. Less WASO on PSG in CBT-I vs control. No other significant differences in actigraphy or PSG measures.**
CBT-I	Miró, et al. 2011[314]	Single site in Spain	44	46.5 (7.03)	100%	SH	90 mins/week for 6 weeks	PSQI	7	90%	High	**PSQI (0-21): CBT-I (-3.5); SH (-0.95) [P<0.05]**	**Improvement in sleep quality with CBT-I.**
CBT-I	Sánchez, et al. 2012[395]	Single site in Spain	26	46.79 (5.15)	100%	SH	90 mins/week for 6 weeks	PSG	6	NI	High	PSG: TST, mins: CBT-I (-9); SH (-34). WASO, mins: CBT-I (-4); SH (0). Sleep efficiency,%: CBT-I (+3); SH (0.83). REM,%: CBT-I (-0.05); SH (+3.41). Stage 1,%: CBT-I (-2.34); SH (+3.41). Stage 2,%: CBT-I (-3.31); SH (-0.2). Stage 3,%: CBT-I (+2.97); SH (+0.12). Stage 4,%: CBT-I (+2.61); SH (-0.89). Arousals, N: CBT-I (+2.63); SH (-0.3). **Deep sleep: CBT-I (+5.55); SH (-0.79).** Light sleep (-5.69); SH (-2.67).	**No increase in sleep time, but increase in time in deep sleep on PSG in CBT-I.**
CBT-IP	Castel, et al. 2012[76]	Single site in Spain	64	49.6 (6.8)	96.9%	TAU	2 hours/week for 14 weeks (3 sessions of CBT-I)	MOS-SS	14	85.90%	High	**MOS-SS Sleep Problems Index (0-100): CBT-IP (+9.4); Control (-0.1) [P<0.001]**	**Improvement in sleep quality with CBT-IP. Improvement maintained at 3- and 6-month follow-up.**
CBT-IP	Lami, et al. 2018[256]	Single site in Spain	84	50.2 (8.2)	100%	TAU	90 mins/week for 9 weeks in groups of 5-7 people	PSQI	9	76.20%	High	PSQI (0-21): CBT-IP (-1.49); TAU (+0.2) [NS]	**No improvement in sleep quality with CBT-IP**

Intervention	Study	Setting	Randomised, N	Age, years	% Female	Control	Treatment duration	Sleep measure(s)	Follow-up, weeks	Completed study, %	Risk of bias	Change from baseline at post-treatment follow-up	Overall result
CBT-P	Saral, et al. 2016[397]	Single site in Turkey	66	Long term (LT): 38.3 (9.8). Short term (ST): 43.2 (9.2). Control: 43.7 (1.1)	100%	TAU	Long term: 180 mins/week for 10 weeks. Short term: 2 190 min sessions	Sleep quality VAS (0-10)	26	89.40%	High	Sleep quality VAS (0-10): CBT-P LT (-4.2); CBT-P ST (-2.1); Control (-0.9)	**No improvement in sleep quality with CBT-P**

Table 2-2. Characteristics and Outcomes of Cognitive Behavioural Therapy Interventions for Sleep Quality in Fibromyalgia.

*This table summarises the study characteristics, treatment protocols, control conditions, sleep outcome measures, and results of cognitive behavioural therapy interventions targeting sleep quality in fibromyalgia patients. Interventions include Cognitive Behavioural Therapy for Insomnia (CBT-I), Pain (CBT-P), and combined CBT-I/CBT-P (CBT-IP), with comparisons against controls such as Sleep Hygiene (SH), Treatment-As-Usual (TAU), and Waitlist Controls (WLC). The primary sleep outcomes include the Pittsburgh Sleep Quality Index (PSQI), Visual Analogue Scale (VAS) for sleep quality, and polysomnography (PSG) measures such as Total Sleep Time (TST), Wake After Sleep Onset (WASO), and Sleep Onset Latency (SOL). Statistically significant improvements are noted in **bold**. Acronyms: CBT-I= Cognitive Behavioural Therapy for Insomnia; CBT-P = Cognitive Behavioural Therapy for Pain; CBT-IP = combined CBT-I/CBT-P; TAU = Treatment-As-Usual; SH = Sleep Hygiene; WLC = Waitlist Control; MOS-SS, Medical Outcomes Study Sleep Scale. PSG = Polysomnography; PSQI = Pittsburgh Sleep Quality Index; VAS = Visual Analogue Scale; TST = Total Sleep Time; WASO = Wake After Sleep Onset; SOL = Sleep Onset Latency.*

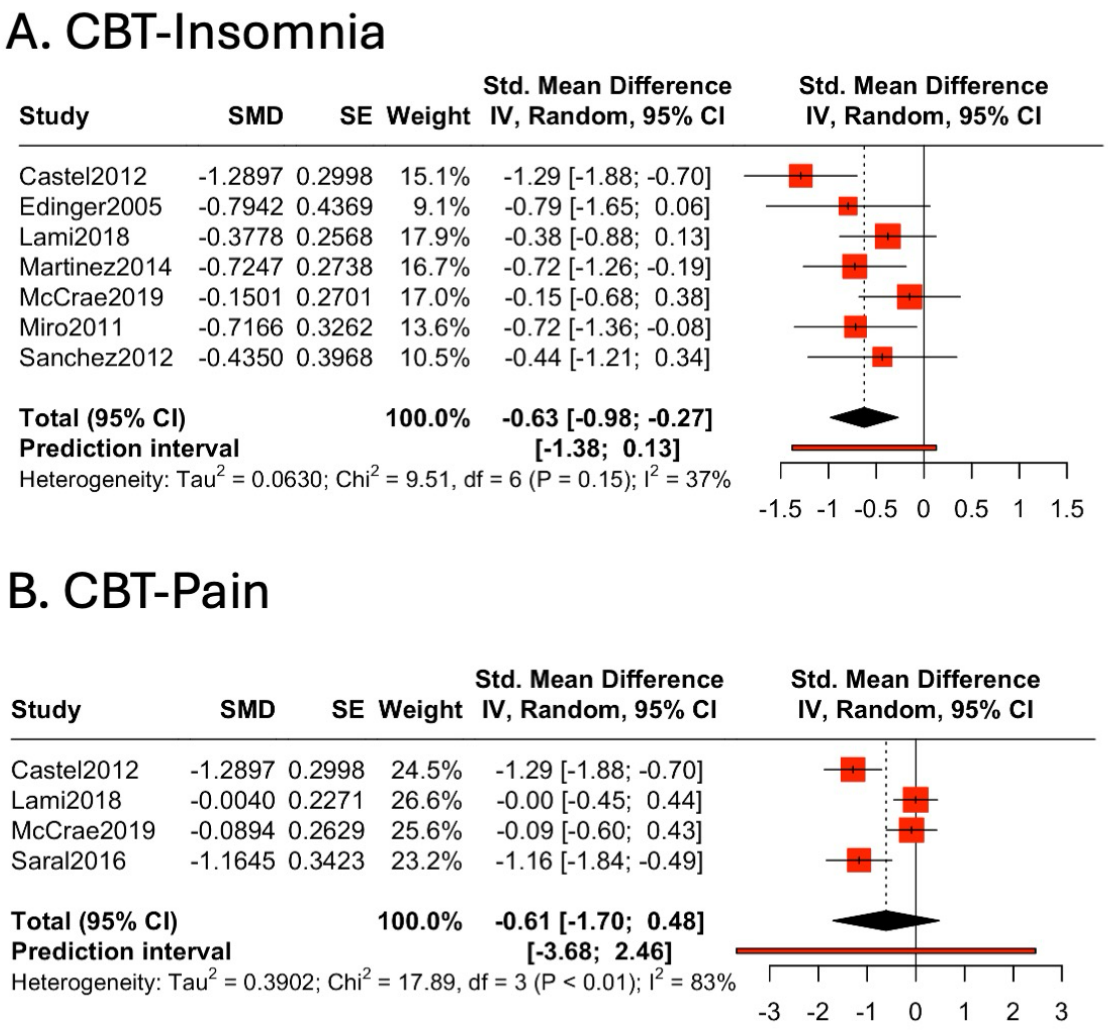


Figure 2-4. Forest plot showing the standardised mean difference (SMD) for the effect of cognitive behavioural therapy for insomnia (CBT-I) on sleep quality in fibromyalgia patients.

The SMD for each study is presented with corresponding standard errors (SE) and 95% confidence intervals (CI). Effect sizes were adjusted to account for baseline differences in sleep quality measures between control and intervention groups. The diamond at the bottom of the plot represents the overall pooled effect, with its width corresponding to the 95% CI. The size of each square is proportional to the weight of the study in the random-effects model. The random-effects model uses the Restricted Maximum Likelihood (REML) method to estimate between-study variance, with Hartung-Knapp (HK) adjustment applied to provide more robust estimates of uncertainty.

2.4 Discussion

2.4.1 Summary

In this systematic review, I find that CBT-I is a promising intervention for improving sleep in fibromyalgia, while pregabalin and sodium oxybate may also be beneficial for this purpose. In contrast, there is no beneficial effect on sleep with amitriptyline, milnacipran, or CBT-P. Other agents, such as gabapentin, quetiapine and zopiclone, demonstrated benefits in individual trials.

2.4.2 Comparison with existing literature

2.4.2.1 Pharmacological agents

TCAs, especially amitriptyline, are commonly used in fibromyalgia treatment. Despite previous literature suggesting that amitriptyline improves sleep quality by promoting sleep onset and continuity[494], I find no evidence that amitriptyline improves sleep quality in fibromyalgia (**Figure 2-3**), consistent with findings in other pain conditions like diabetic neuropathy[60]. High heterogeneity and a wide prediction interval highlight uncertainty.

Gabapentinoids, particularly pregabalin, have been another mainstay of fibromyalgia treatment. Pregabalin improves sleep across a range of clinical conditions[382] through a direct effect on sleep rather than mediated by improvements in pain or other symptoms[386]. Compared to hypnotic agents, pregabalin appears to enhance slow-wave sleep (SWS) in addition to increasing sleep continuity[200]. This is of particular

relevance to fibromyalgia, where a reduction in SWS has been noted[61; 372]. However, concerns about adverse events and abuse, especially in combination with opioids[145], have led NICE to stop recommending pregabalin for fibromyalgia (NG193[2]). While this review supports pregabalin's effectiveness in improving sleep (**Figure 2-3**), in line with previous reviews[435], these benefits must be weighed against the relatively modest effect size and its potential for misuse.

Sodium oxybate, a gamma-aminobutyric acid antagonist, has been shown to increase SWS and improve sleep continuity in both healthy and clinical populations[349]. Although it may have some benefit for sleep in fibromyalgia (**Figure 2-3**), the evidence is limited, and concerns about its potential for misuse limit its use in fibromyalgia management.

Among other first-line treatments for fibromyalgia[195], duloxetine has the least evidence supporting its effect on sleep. Only one study was included in this review, which found no improvement in sleep quality, which is notable given the significant sleep disturbances experienced by fibromyalgia patients.

2.4.2.2 CBT

This review finds a moderate beneficial effect of CBT-I on sleep quality in fibromyalgia (**Figure 2-4**), updating findings from a previous review of the topic[98]. This is in keeping with findings for CBT-I in other musculoskeletal pain disorders[393] and in insomnia generally[453]. Sleep restriction therapy, where time in bed is limited to actual sleep

time, is thought to be the "active" component of CBT-I[294]. Although CBT-I is recommended as the first-line treatment for insomnia, evidence of its impact on objective PSG measures of sleep is limited[315], which is reflected in this review. Variations in CBT-I programs, outcome measures, and control arms (e.g., sleep hygiene or no intervention) present challenges. Scaling CBT-I is also challenging due to a shortage of trained clinicians, but digital CBT-I is a promising alternative, with effectiveness comparable to face-to-face therapy[424]. However, special considerations should be given to co-morbid symptoms common in fibromyalgia, particularly brain-fog and fatigue, as they may be a barrier to engaging with these interventions.

Of particular relevance to this thesis, one trial of CBT-I, by Miró et al.[314], evaluated its effect on cognitive performance, suggesting that CBT-I may lead to clinically meaningful improvements in specific cognitive domains, alertness and executive control, in individuals with fibromyalgia. The absence of change in the orienting index suggests that these effects may be domain-specific. Of interest, improvements in executive function were associated with better sleep quality. While between-group effects were not formally tested, the moderate-to-large within-group improvements observed in the CBT-I group suggest that sleep interventions may hold clinical value in improving cognitive performance, particularly executive function, in fibromyalgia. However, the study was a small pilot trial involving a relatively homogenous sample (middle-aged women with fibromyalgia), which limits the generalisability of findings. There was also considerable attrition for the cognitive outcome, with only 31 of 44 participants (70.5%) completing the follow-up ANT-I, increasing the risk of bias.

Additionally, subjective cognitive complaints were not assessed, limiting insight into the relationship between objective performance and perceived cognitive dysfunction or “brain fog”. Finally, the study relied solely on self-reported sleep quality; no objective sleep measures (e.g., actigraphy or polysomnography) were obtained, preventing examination of the relationship between objective sleep disturbance and cognitive change.

In contrast, CBT-P showed no beneficial effect on sleep (**Figure 2-4**). While CBT has a role in improving mood and coping with pain in fibromyalgia[41; 46], its effects on sleep are less clear. This suggests that non-pharmacological therapies aimed at improving sleep should focus directly on sleep (i.e., CBT-I) rather than indirectly through mood or pain. Notably, combined CBT-I/CBT-P interventions did not show greater benefits than CBT-I alone. Further research comparing combined CBT-I/CBT-P with standalone CBT-I would be valuable for guiding fibromyalgia management.

2.4.3 Strengths and limitations

The strengths of this review include a comprehensive evaluation of both pharmacological and CBT interventions for sleep in fibromyalgia. Notably, this study is one of few to evaluate the efficacy of both CBT-I and CBT-P, underscoring CBT-I’s specific benefits for sleep quality in fibromyalgia.

This review has several limitations. Variability in intervention protocols, outcome measures, and control conditions limits comparability and interpretation. Most

pharmacological studies prioritised pain as the primary outcome, which may reduce the specificity of sleep-related findings.

In CBT trials, the lack of blinding and heterogenous control conditions complicates direct comparisons. Although continued medication use during CBT allows a more practical assessment of improvements, it may also add variability.

Sleep assessments varied, with an assortment of both subjective tools (e.g., MOS-SS, JSS, VAS) and objective measures (e.g., PSG, actigraphy) employed. Subjective measures, like VAS/NRS scales, are thought to reflect how refreshed participants feel, and may be biased by participants' awareness of the study focus on sleep[469]. Furthermore, mood or cognitive factors, such as depression or catastrophising tendencies, which are common in conditions like fibromyalgia, may also influence responses and amplify perceived sleep disturbance, even when objective sleep parameters remain unchanged. Conversely, tools such as actigraphy and PSG offer quantifiable measures of sleep architecture, duration, and efficiency, which are less subject to participant bias. PSG is considered the gold standard for measuring sleep physiology, but is limited by its cost and the burden it places on subjects. Actigraphy is more accessible and less intrusive, although it lacks the granularity of PSG and may inaccurately classify periods of inactivity as sleep[102]. This may be a particular problem in conditions with fragmented sleep patterns, such as fibromyalgia[53]. Despite their limitations, self-reported sleep measures are clinically relevant, as they reflect the patient's experience and may better align with treatment goals, such as improving perceived sleep quality and overall satisfaction[250].

A lack of long-term follow-up data restricts conclusions about the sustainability of treatment effects on sleep, highlighting the need for future studies to use standardised sleep outcome measures over extended follow-up periods.

2.4.4 Implications for research and clinical practice

This review supports CBT-I as a first-line treatment for insomnia in fibromyalgia, though more research is needed to identify the most effective modalities and doses. Given barriers to face-to-face delivery, digital CBT-I may be a promising option in fibromyalgia, although work is needed in this area. In contrast, CBT-P is unlikely to benefit sleep, though it may help with other symptoms.

Pharmacotherapy should not be a first-line treatment for sleep disturbance in fibromyalgia. Agents widely considered to improve sleep, like amitriptyline and duloxetine, show no beneficial effects, while pregabalin, though potentially helpful, carries risks of misuse and should be used with caution. A better understanding of the aetiopathogenesis of fibromyalgia is necessary to aid future drug development focus on more specific targets with fewer side effects.

Stratifying patient populations by genetic and environmental risk factors could improve treatment outcomes. Future studies should use both standardised self-reported sleep quality assessments and objective measures like actigraphy and PSG to better understand how sleep treatments work. Furthermore, studies should focus on

outcomes beyond pain and insomnia, and assess treatments broader impact on quality of life[328].

3 Chapter Three: Relationship between nociplastic pain severity and executive function in UK Biobank

3.1 Introduction

Self-reported, or subjective, cognitive difficulties (e.g. 'brain-fog') are commonly reported by people with chronic pain conditions, and forms a part of nociplastic pain syndromes, such as fibromyalgia[326]. Executive function—a set of cognitive processes including working memory, flexible thinking, and self-control—is essential for regulating behaviour, decision-making, and goal-directed actions[171]. Individuals with chronic pain often report difficulties in these areas, experiencing problems with concentration, memory, and mental clarity[38].

However, as discussed in Chapter 1, the association between pain and cognitive decline is less certain (**section 1.3.2.2, Table 1-1**). Most studies have focused on memory or dementia risk[492]. However, although some studies suggest that pain is associated with a decline in executive functions such as psychomotor speed[40; 385], others have not[462; 470]. This may be due to measurement error in individual cognitive tests, or insufficient phenotyping of pain characteristics. In particular, the association between nociplastic pain severity and deterioration in executive function has not previously been examined.

Symptoms in chronic primary pain disorders, which are driven by nociplastic pain, cluster into two groups: (1) generalised sensory sensitivity and (2) sleep, pain, affect (depression/anxiety), cognition (brain-fog), energy/fatigue (SPACE)[402]. These

symptoms may account for the impaired cognitive performance observed in chronic pain.

The characteristics and quality of pain itself may also play an important role in executive dysfunction in chronic pain. Pain can disrupt cognition by monopolising attentional resources, an effect that may be influenced by the intensity, distribution, or qualities of the pain[466].

The use of analgesics has also been suggested as a link between chronic pain and poor cognition. A recent large cohort study of older adults identified a small decline in cognitive function associated with opioid prescription[482]. However, systematic reviews of the topic are conflicting: finding that opioid use is associated with both improvement and impairment in cognition[234; 351]. Cognitive difficulties are commonly reported by patients prescribed gabapentinoids, which have been linked to a decline in cognitive function in older adults[339]. There is also suggestive evidence that tricyclic antidepressants, such as amitriptyline, which are commonly used in the management of chronic pain, are linked to cognitive dysfunction in both the management of depression[148; 444] and pain disorders such as postherpetic neuralgia[355].

Overall, it remains unclear whether these symptoms mediate an association between pain and objective executive dysfunction, and how they interact with one another.

3.1.1 Aims and hypotheses

Aim 1: To investigate the relationship between nociplastic pain severity and executive function in UK Biobank, a large cohort of middle-age British adults.

3.1.1.1 Aim 1: Hypotheses:

A. Adults with *chronic pain* have *worse* executive function compared to those with no chronic pain.
B. *Nociplastic pain severity*, measured by the Fibromyalgia Index (FMI), is associated with *worse* executive function in adults with chronic pain.
C. Nociplastic pain severity is associated with a faster rate of *decline* in executive function over time.

Aim 2: To examine the mediating role of the SPACE symptom cluster, pain characteristics, and analgesia use in the relationship between nociplastic pain severity and executive function.

3.1.1.2 Aim 2: Hypotheses

A. The SPACE symptom cluster (sleep, pain, affect, cognition, and energy) mediates the relationship between nociplastic pain severity and executive function.
B. Pain characteristics (pain severity, neuropathic qualities, and widespread pain) mediate the relationship between nociplastic pain severity and executive function.
C. Analgesia use (opioids, tricyclic antidepressants, and gabapentinoids) mediates the relationship between nociplastic pain severity and executive function.

3.2 Methods

3.2.1 Overview of UK Biobank

UK Biobank is a multi-centre prospective cohort study[10]. Adults aged between 40 and 69 registered with the National Health Service (NHS), and living within 25 miles of one of 22 assessment centres in Great Britain, were invited. Of an eligible population of approximately 9 million adults, approximately 500,000 individuals gave written consent and participated in a baseline visit between 2006 and 2010. During follow-up, approximately 330,000 participants for whom UK Biobank have a current email address were invited to complete online questionnaires on various topics, including chronic pain. In addition, UK Biobank aims to image 100,000 participants during follow-up at four imaging centres: Stockport, Newcastle-upon-Tyne, Reading, and Bristol. Visits commenced in Stockport first, in April 2014, followed by Newcastle-upon-Tyne in April 2017, Reading in June 2018, and Bristol in February 2020. Initially, all participants for whom UK Biobank had a current email address were invited, but in 2020 postal invitations to the entire cohort were commenced. A small number (<0.5%) of participants who no longer wish to be contacted or have left the UK were not invited[273].

The main UK Biobank study received ethical approval from the NHS National Research Ethics Service (Ref. 11/NW/0382). The present study was approved as UK Biobank application number 45465.

3.2.2 Setting and Study population

This was a cohort study set within UK Biobank (**Figure 3-1)**. Participants were eligible if they completed a cognitive assessment in 2017–2020 and an online pain questionnaire in 2019 , as the latter included the FMI for evaluating nociplastic pain severity, and the cognitive assessment was closest temporally to the questionnaire. Participants assessed before December 2016, before the expanded cognitive battery was introduced, were excluded. To evaluate changes in cognition over time, those who also completed an online cognitive assessment in 2021–2022 were included. Participants with a self-reported or documented healthcare record of dementia, or serious neurological condition, which may affect pain reporting, were excluded.

3.2.3 Questionnaires

In 2017-2020, participants completed questionnaires on lifestyle, family, and social history, and a series of cognitive tasks, on a touchscreen, with additional clinical data collected by a research nurse. In 2019, participants completed an online pain questionnaire. These timepoints served as the baseline for this study.

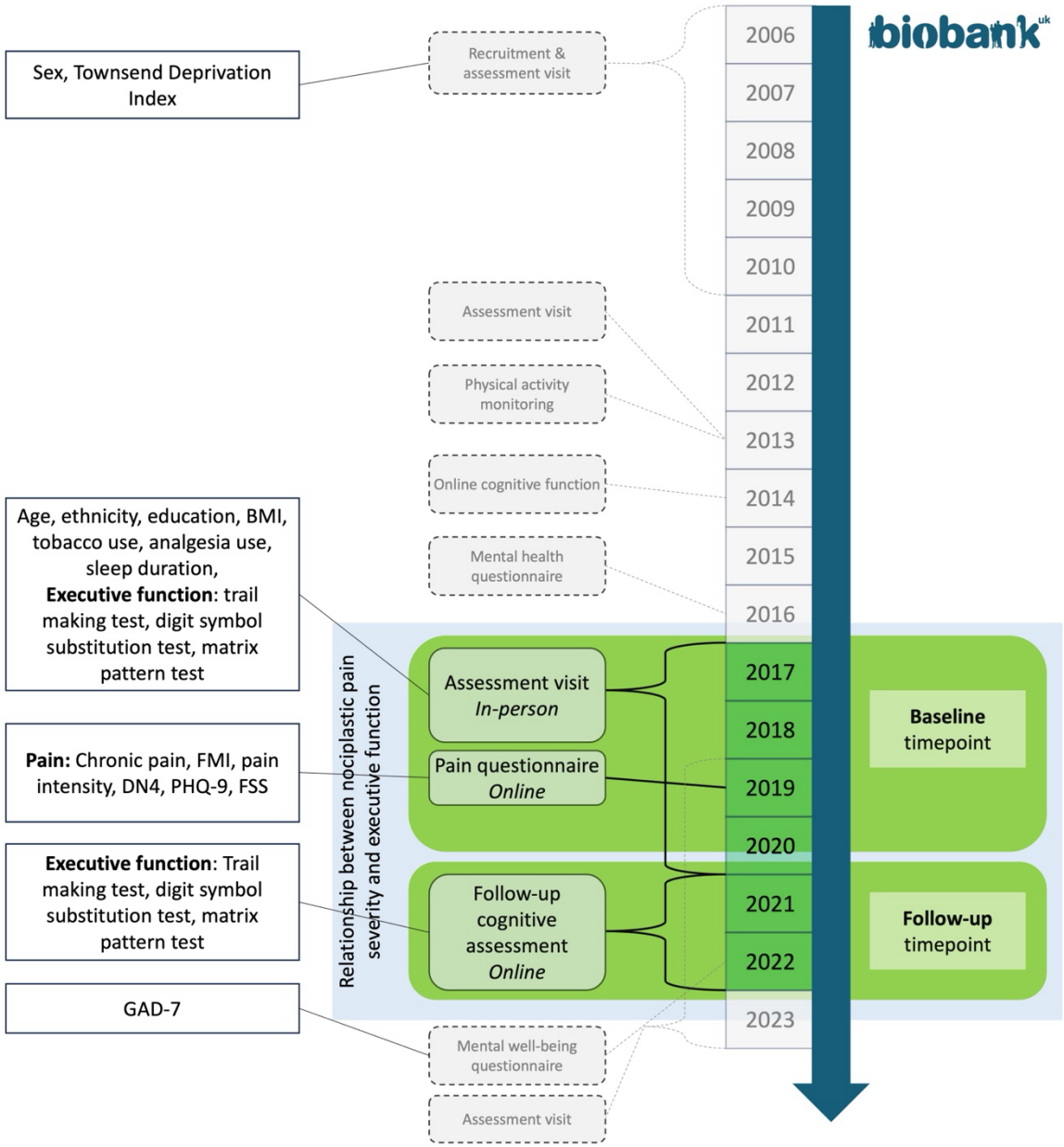


Figure 3-1. Flow diagram of UK Biobank assessments.

A flow diagram of the timeline for the main assessments in UK Biobank. The assessments used in the current study are highlighted in green. All participants for whom UK Biobank had a current email address (~333,000) were invited to attend follow-up visits and complete online questionnaires. Commencing 2020, UK Biobank began sending postal invitations for the follow-up imaging visit. A small number (<0.5%) of participants have withdrawn or moved outside the UK. An expanded battery of cognitive assessments was introduced in imaging visits conducted after December 2016, and participants who attended the imaging visit prior to this were not included. The cognitive assessment undertaken during the first imaging visit between 2017 and 2020 was taken was the baseline timepoint for this study. The online pain questionnaire taken in 2019 was taken as the baseline assessment for pain. The online cognitive assessment performed in 2021-2022 was the follow-up assessment for this study. Sex and Townsend deprivation index were only assessed at recruitment. As no validated measure of anxiety was assessed at the time of the imaging visit or pain questionnaire, the GAD-7 from the 2022 mental well-being questionnaire was used. For the cross-sectional analysis, participants who completed cognitive tests at the first imaging visit and the experience of pain questionnaire were included. For the longitudinal analysis, participants who subsequently also completed the follow-up online cognitive assessment were included. BMI, body mass index. FMI, fibromyalgia index. DN4, douleur neuropathique 4. PHQ-9, patient health questionnaire 9-item. FSS, fatigue severity scale. GAD-7, general anxiety disorder 7-item.

3.2.3.1 Pain

In the 2019 pain questionnaire, participants were asked about the presence of pain or discomfort for more than three months. Those who answered “yes” were classified as having chronic pain. The questionnaire also included the 2016 revised Fibromyalgia Survey Criteria (FSC). This comprises the widespread pain index (WPI, 0-19) and symptom severity scale (SSS, 0-12)[499]. Nociplastic pain severity can be measured using the FSC as a continuum, referred to here as the Fibromyalgia Index (FMI, 0-31)[159; 499]. The FMI has demonstrated predictive value for pain outcomes after surgery and pain relief from opioids following arthroplasty[65] and hysterectomy[217].

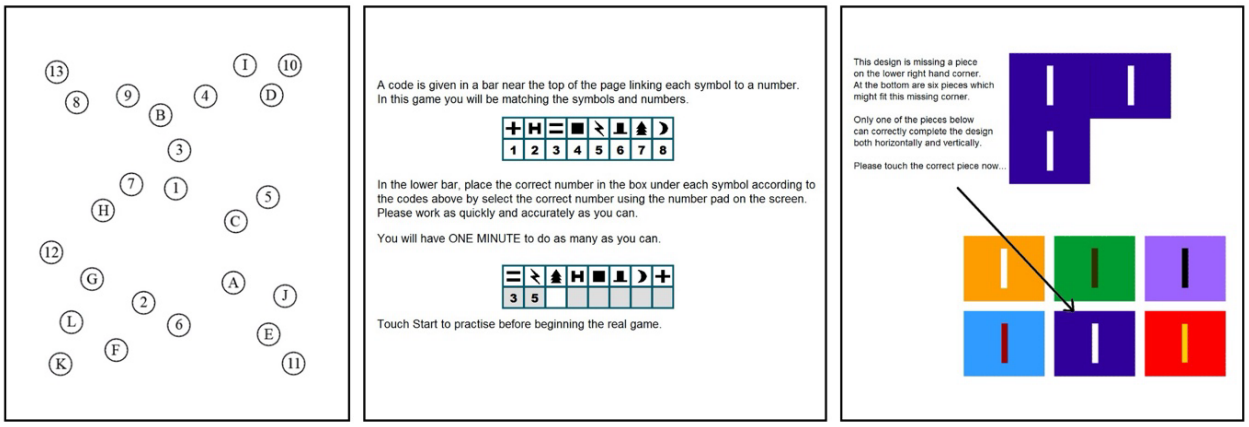
3.2.3.2 Executive function

Participants completed a series of cognitive tasks on a touchscreen interface (**Figure 3-2**). The baseline cognitive assessments from 2006–2010 were excluded from this study due to their temporal distance from the 2019 pain questionnaire, as well as their rudimentary nature, limited ability to measure executive function, modest stability[280]. The UK Biobank cognitive assessment was subsequently revised and expanded in December 2016 during the imaging visit. These updated assessments were conducted in person in 2017-2020 and repeated online in 2021-2022. This study analysed three cognitive tests designed to assess aspects of executive function (**Figure 3-2**):

- **Trail Making Test (TMT)**. Participants completed two paths on a touchscreen. For the numeric path (Trail #1), numbers were selected in ascending order (e.g., 1-2-3). For the alphanumeric path (Trail #2), participants alternated between

numbers and letters (e.g., 1-A-2-B). The difference in completion times (milliseconds) between the two paths measured executive function.

- **Digit-symbol Substitution (SDS)**. Participants matched symbols to their corresponding digits using a reference grid, completing as many as possible within 60 seconds. Performance was measured as the proportion of correct responses.
- **Matrix Pattern Recognition**. Participants solved puzzles by selecting the option that completed a logical matrix pattern. Tasks increased in difficulty, and performance was measured as the proportion of correct responses.



A. Trail Making Test B. Digit-Symbol Substitution Test C. Matrix Pattern Recognition Test

Figure 3-2. Cognitive tests from UK Biobank used to assess executive function.

(A) Trail Making Test (TMT): Participants alternated between numbers and letters in ascending order (e.g., 1-A-2-B) to measure executive function.

(B) Digit-Symbol Substitution (SDS): Participants matched symbols to digits using a reference grid within 60 seconds, assessing processing speed and attention.

(C) Matrix Pattern Recognition Test: Participants completed puzzles by selecting the missing piece to match a logical pattern, measuring abstract reasoning. Images adapted from the UK Biobank showcase.

3.2.3.3 Confounding variables

Confounders were selected *a priori* based on evidence of association between nociplastic pain and cognition[230]. Baseline socio-demographic data included age (years), sex (male, female), ethnicity (white, non-white), Townsend index of material deprivation (comprised of four factors: unemployment, car ownership, home ownership, and household overcrowding; higher values indicate greater material deprivation)[450], and education (university degree, no degree). Lifestyle variables included tobacco use (current or never/former), and body mass index (BMI, kg/m^2).

3.2.3.4 Mediators

Three groups of mediators were considered: SPACE, pain and analgesics.

3.2.3.4.1 SPACE Cluster

The SPACE cluster of symptoms, sleep, pain, affect, cognition, and energy/fatigue[402] were considered as mediators.

1) Participants reported how many hours they slept in a 24-hour period, including naps. Given the U-shaped association between sleep duration and cognitive outcomes, I binarised sleep into normal (7-9 hours) and abnormal (<7 or >9 hours) sleep duration, based on Sleep Research Society guidelines for the recommended sleep duration[484].
2) Pain intensity was measured using a 11-point numeric rating scale on the pain questionnaire. Participants were asked to rate the scale of pain that bothered them most in the last 24 hours in their worst body area on a scale from 0 (“no pain”) to 10 (“worst pain”).

3) Depression symptoms were measured using the Patient Health Questionnaire 9 (PHQ-9, 0-28)[248] from the 2019 pain questionnaire. As no validated measure of anxiety symptoms was used at the 2017-2020 imaging visit or 2019 pain questionnaire, the Generalised Anxiety Disorder scale 7 (GAD-7, 0-21)[430] from the 2022 mental well-being questionnaire was used. Higher scores on both items indicate more severe symptoms.
4) Cognitive symptoms were measured using the item on subjective cognitive difficulties from the SSS[499]. Participants were asked to rate the level of severity of cognitive symptoms such as problems with memory, thinking skills and/or concentration. Responses included 1 ("No Problem"), 2 ("Slight or mild problems: generally mild or intermittent), 3 ("Moderate: considerable problems; often present and/or at a moderate level") and 4 ("Severe: pervasive, continuous, life disturbing problems").
5) Energy was measured using the Fatigue Severity Scale (FSS, 9-63)[249], a 9-item instrument which assesses the severity of fatigue. Higher scores indicate more severe fatigue.

For analysis, continuous variables were standardised to a mean of 0 and SD of 1.

3.2.3.4.2 Pain characteristics

To understand which pain characteristics play a role in executive dysfunction in nociplastic pain, three characteristics were examined. This included (1) pain intensity

(described above in section 3.2.3.4.1), (2) the Douleur Neuropathique 4 (DN4), and (3) the WPI.

The DN4 is a self-report, a seven-item questionnaire on neuropathic pain quality[59]). While the DN4 is typically used to diagnose neuropathic pain, it may also indicate central sensitisation, a key feature of nociplastic pain[390].
The WPI, a component of the 2016 FSC was included as a measure of bodily distribution of pain. Widespread pain is also a sensitive marker of nociplastic pain[159].

3.2.3.4.3 Analgesia use

During the 2017–2020 visit, participants who reported taking prescription medications provided a list during the interview with a research nurse. Participants were categorised based on self-reported use of analgesics commonly prescribed for nociplastic pain disorders:

- **Opioids**: Weak (e.g., codeine, tramadol) or strong (e.g., morphine, oxycodone).
- **Tricyclic antidepressants (TCAs)**: Amitriptyline, nortriptyline.
- **Gabapentinoids**: Pregabalin, gabapentin.

Item codes are provided in
Supplementary Table B-2. As up-to-date healthcare record linkage to prescription data was unavailable, these classifications rely on self-reported data and may be subject to recall bias.

3.2.4 Statistical Analysis

The response rates for each assessment were calculated and presented in a flow diagram. Descriptive baseline characteristics of included participants were summarised using means and standard deviations (SD) for continuous variables, and frequencies with proportions for categorical variables, overall and stratified by chronic pain status. Characteristics of participants lost to follow-up between baseline and follow-up cognitive assessments are detailed in Supplementary Table B-4.

3.2.4.1 Confirmatory Factor Analysis

Confirmatory factor analysis (CFA) was conducted to estimate a latent measure representing the three cognitive tests described in section 3.2.3.2. This approach has the advantages of allowing the representation of multiple related measures together, while minimising measurement error[54; 55; 270]. CFA tested whether a pre-specified model of observed variables fits with an underlying construct, in this case, executive function. Fit indices were used to evaluate the plausibility of the hypothesis CFA model, including the comparative fit index (CFI), Tucker Lewis index (TLI), and root square mean error of approximation (RMSEA). These indices assess how well the specified factor structure accounts for the covariance among the observed variables. CFI and TLI values >0.90, and RMSEA values <0.05, indicate good model fit.

This approach aligns with previous applications in UK Biobank, where CFA-derived measures of cognitive constructs have demonstrated acceptable model fit and good correlation with those derived from gold standard neuropsychological assessments[151; 280; 442; 467].

What my study adds is that, in addition to cross-sectional CFA, I also perform longitudinal CFA and assess the factorial invariance of executive function across time points in UK Biobank. This method extends CFA by assessing whether the same latent construct, executive function, is measured at different time points. This concept is termed factorial invariance, and ensures that observed changes are due to true differences in the underlying construct rather than shifts in measurement properties[495]. This is particularly important in the context of cognition, where changes may be due to evolving test characteristics over time, as opposed to genuine underlying cognitive shifts[493].

3.2.4.1.1 Data preparation

Outliers in the trail making test (>|3| SD) were winsorised by capping values within the observed range. This approach reduced the influence of extreme values, which may reflect measurement error or rare but valid individual differences, on model specification.

Given the strong confounding influence of age on cognitive performance, which was not of primary interest in the present study, the individual cognitive tests were adjusted for age prior to CFA[104]. To account for the varying impact of age across tests, polynomial regression was used to model the relationship between age and each test. Polynomial fits of increasing degrees were compared using likelihood ratio tests to identify the model which best captures the relationship with age. At baseline, quadratic models fit the SDS and matrix pattern tests, while a cubic model fit the TMT; at follow-up, a linear

model fit the SDS test, a quadratic model fit the TMT, and a cubic model fit the matrix pattern test. Residuals from these models, representing variance in test scores independent of age, were extracted. This adjustment effectively removed age-related variance, as confirmed by near-zero coefficients and nonsignificant associations with age in the adjusted models.

The variables were then re-scaled using the proportion of maximum scaling (POMS) method to give a common scale of 0 to 1, to reduce model misspecification which may occur when variables on different scales are included in factor analysis[270]. TMT scores were reverse coded so that higher scores indicated better cognitive performance across all tests.

To aid interpretation and communication of results, the cognitive test outcomes and latent factor for executive function were also transformed into centile ranks, where the 1st centile is the worst performer, and the 100th centile is the best performer[108].

3.2.4.2 Aim 1A&B: Cross-sectional CFA

The cross-sectional relationship between nociplastic pain severity (FMI) and executive function (EF) was assessed using a latent factor for EF as the primary outcome (Section 3.2.4.1). EF centile rank was included as a secondary outcome for ease of interpretation. A three-item CFA model was constructed using the cognitive tests detailed in Section 3.2.3.2.

Linear regression was performed with mean-centred continuous variables and dummy-coded categorical variables.

Analyses were stratified by chronic pain status to account for overlap between symptoms included in the FMI such as depression, sleep disturbance, fatigue, and brain-fog, and symptoms that may occur in individuals without chronic pain.

Within the chronic pain group, secondary analyses stratified by sex were conducted to explore effect modification due to known sex differences in pain perception and cognitive outcomes. Interaction terms were tested using likelihood ratio tests (LRT) to evaluate whether the relationship between FMI and EF differed by chronic pain status or sex.

Within each stratification, two models were assessed:

1. **Minimally adjusted model**: adjusted for age, sex, and time between pain and cognitive assessments.
2. **Fully adjusted model**: further adjusted for socioeconomic deprivation, ethnicity, education, smoking status, and BMI.

Potential non-linear effects of the time elapsed between pain and cognitive assessments on EF were modelled using polynomial terms (linear, quadratic, and cubic). Model fit was evaluated using visual inspection and likelihood ratio tests to compare linear and higher-order terms. The best-fitting model ($P<0.05$ for higher-order terms) captured the complexity of how the timing between pain and cognitive assessments influences executive function, accounting for potential non-linear trends.

Model assumptions were checked, including linearity of continuous covariates, normality of residuals, and homoscedasticity. Multicollinearity was assessed using generalised variance inflation factor (GVIF) in order to handle variables with multiple degrees of freedom.

3.2.4.3 Aim 1C: Longitudinal CFA

3.2.4.3.1 Longitudinal stability of executive function

To assess the factorial invariance and longitudinal stability of executive function over time, longitudinal CFA was conducted using the three cognitive tests described in section 3.2.4.1. A two-factor, three-item CFA model was constructed[270], with residual covariances estimated between the same tasks across time.

Measurement invariance was assessed by fitting four CFA models with progressively stricter constraints:

1. **Configural invariance**: Allowed freely estimated factor loadings, intercepts, and item variances across both time points.
2. **Weak (metric) invariance**: Constrained factor loadings to be equal across time, while intercepts and variances were freely estimated.
3. **Partial strong (scalar) invariance**: Constrained factor loadings of all variables, and intercepts of SDS and matrix pattern test to be equal across both time points, allowing the TMT intercept to vary.
4. **Strong (scalar) invariance**: Constrained all factor loadings and intercepts to be equal across time, allowing only item variances to vary.

Models were fitted using robust maximum likelihood estimation. Model fit was assessed using the robust CFI, TLI, RMSEA, and Standardised Root Mean Square Residual (SRMR). Incremental changes in fit indices were used to determine invariance between models[495]. A threshold of ≤0.01 for ΔCFI and ΔTLI[86], ≤0.015 for ΔRMSEA[80], and ≤0.03 for ΔSRMR[389] was used to assess invariance between models.

3.2.4.3.2 Aim 1C: Longitudinal relationship between nociplastic pain severity and executive function

Within the chronic pain group, the relationship between the FMI at baseline and EF at follow-up, controlling for baseline EF, was investigated using structural equation modelling (SEM). SEM allows for simultaneous estimation of the latent (measurement) and structural models, maintaining consistency and avoiding loss of information from the original CFA. Two longitudinal models were assessed: (1) adjustment for age and sex, (2) and full adjustment for an *a priori* selection of socio-demographic and lifestyle confounders, as described in section 3.2.4.2. The direct effect of interest was from FMI score at baseline to EF at follow-up, with an indirect pathway via baseline EF. Models were fitted using robust maximum likelihood estimation. Model fit was assessed using CFI, TLI, and RMSEA.

3.2.4.4 Aim 2: Mediation analyses

Mediation analysis was conducted using SEM to estimate the direct and indirect effect of the mediators on the association between FMI and EF at baseline and follow-up,

within the chronic pain group. Mediation analysis identifies how an independent variable influences a dependent variable through one or more mediators, consistent with the framework established by Baron and Kenny[29]. SEM was chosen for its ability to simultaneously model latent variables and structural pathways, as well as account for measurement error[271]. Direct, indirect, and total effects were estimated using bias-corrected bootstrapping with 5,000 resamples to test the significance of the mediation pathways, which accommodates non-normal distributions of indirect effects[85].

Three mediation models were evaluated:

- SPACE symptoms (Aim 2A): Short/long sleep duration, pain severity, affect (depression and anxiety), cognitive symptoms (brain-fog), and energy problems (fatigue).
- Pain characteristics (Aim 2B): Pain severity (NRS), widespread pain (WPI), and neuropathic pain (DN4).
- Analgesia use (Aim 2C): Use of opioids, TCAs, and gabapentinoids.

For each model, the direct effect represents the remaining association between FMI and follow-up EF not explained by baseline EF or the mediators. The indirect effects quantify the influence of each specific mediator pathway, and the total effect provides an aggregate measure, incorporating both direct and indirect pathways. Covariances between mediators were included to capture their interrelated nature. Total effects combined direct and indirect pathways. Age, sex, socio-demographic factors (SES, ethnicity, education), and lifestyle variables (tobacco use, BMI) were included to adjust for potential confounding.

3.2.4.5 Missing data

The response options “prefer not to answer” and “do not know” were classified as missing values. Incomplete follow-up data were present for several components, including the 2017-2020 cognitive assessment, the 2019 pain questionnaire, and the 2021-2022 online cognitive assessment, due to participant non-response. Given the high proportion of non-response (~50% for the pain questionnaire, and >80% for imaging assessment), multiple imputation would be unsuitable as it assumes data is missing at random.

Additionally, a further subset of participants lacked cognitive test data from the imaging assessment, as these tests were introduced in December 2016. For participants with missing data, complete case analysis was performed.

3.2.5 Sensitivity analyses

Sensitivity analyses examined the association between FMI and each of the three cognitive tests (section 3.2.3.2) and explored potential biases due to the timing of cognitive assessments relative to the COVID-19 pandemic and the time lag between cognitive and pain assessments.

3.2.5.1 Individual cognitive tests

Each cognitive test was analysed separately as an outcome using linear regression models with the covariates described in section 3.2.4.2. Age-adjusted cognitive scores were the outcomes.

3.2.5.2 Timing discrepancies between cognitive and pain assessments

Variability in the timing between baseline cognitive assessments and the pain questionnaire was addressed through stratified analyses:

- **Relative timing of assessments**: Participants were grouped by whether the pain questionnaire was completed before or after the cognitive assessment. This binary classification provided a broad sense of whether the relative timing of pain and cognition assessments influenced observed associations.
- **Time band stratification**: Participants were further classified into one-year intervals between the pain questionnaire and cognitive assessment to capture trends or patterns over time.

These analyses aimed to determine if the time interval between assessments influenced the strength or direction of the relationship between FMI and EF.

3.2.5.3 Stratification by COVID-19 period

The COVID-19 pandemic may have impacted cognitive performance due to potential direct effects of the virus or indirectly through factors such as social isolation and disturbed mental health[520]. To evaluate whether cognitive function was differentially affected in participants tested before versus after the onset of the COVID-19 pandemic, analyses were stratified into two groups to assess for potential effect modification between COVID-19 and FMI on EF:

- **Pre-COVID group**: Cognitive assessments completed before 1st March 2020.
- **Post-COVID group**: Cognitive assessments completed from 1st March 2020 onward.

Data are reported according to the STROBE guidelines[170]. Data preparation and descriptive analyses were performed using the `dplyr`, `tidyr`, `MASS`, `jtools`, `emmeans`, and `stats` packages. Likelihood ratio tests were performed using the `lrtest()` function from the `lmtest` package. GVIF was tested using the `vif()` function from the `car` package. CFA, SEM and mediation analyses were performed using the `cfa()` and `sem()` functions from the `lavaan` package v0.6-18. Data visualisation was carried out using `ggplot2` and `ggpubr`. Analyses were conducted in R version 4.4.1. Standardised parameter estimates with bootstrapped 95% confidence intervals are reported. Two-sided P-values with significance set at $P<0.05$ were used for all analyses. All field ID codes used in the analysis are found in **Supplementary Table B-1**.

3.3 Results

3.3.1 Study participants

Of 502,369 UK Biobank baseline participants, 335,587 (66.8%) were sent an email invitation, of whom 167,185 (49.8%) completed the follow-up pain questionnaire in 2019. As of early 2020, 44% of UK Biobank participants were invited to attend an imaging visit, of whom 53% did not respond and 17% declined the invitation. Of the 31% who responded, 71% were eligible, and 97% attended a visit[273]. Approximately 177,000 participants completed the online cognitive assessment in 2021-2022 (responses varied slightly across individual tasks). This represents just over half of participants with a current email address, and is a similar response rate to the online pain questionnaire.

Of the participants who completed the pain questionnaire, 50,763 (30.4%) also attended the imaging assessment (**Figure 3-3**). Of this group, 15,119 (29.8%) were excluded due to missing cognitive test data, as these were introduced in December 2016, partway through the imaging assessment visits. A small number were excluded due presence of major neurological condition (n=136; 0.3%) or missing pain (n=489; 1%) or covariable (n=221; 0.4%) data. This left 35,423 (69.7%) participants in the cross-sectional analysis. Of these, 18,898 (53.3%) subsequently completed the online cognitive assessment, with a median (range) follow-up of 2.69 (1.07 to 4.43) years, and were included in the longitudinal analyses.

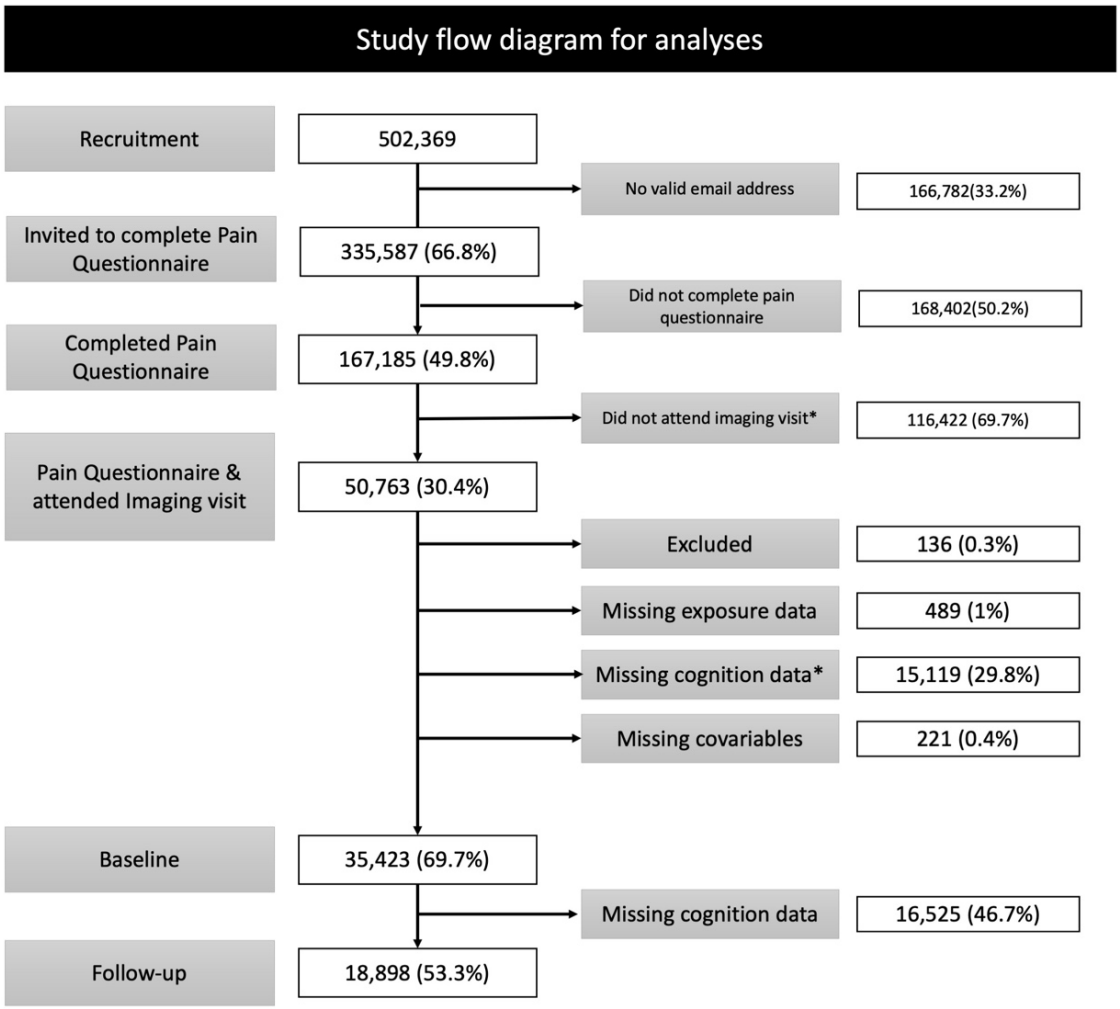


Figure 3-3. Study flow diagram for UK Biobank participants in cross-sectional and longitudinal analyses of relationship between FMI and executive function.

3.3.2 Baseline characteristics

Baseline characteristics for participants included in the cross-sectional analysis are presented in **Table 3-1**. The mean age was 64.5 years (SD 7.4), and 52% of participants were female. At baseline, 53% (18,769) reported chronic pain in at least one site (median 2, IQR 1-2), with a significantly higher mean FMI score of 5.04 (SD 3.91) in the chronic pain group compared to 1.96 (SD 1.93) among those without chronic pain.

Chronic pain was more prevalent among females (56% vs 49%, P<0.001), individuals with lower educational attainment (50.6% with a degree vs 55.5% without, P<0.001), and those with higher BMI (mean 26.8 kg/m^2 vs 25.9 kg/m^2, P<0.001). Participants with chronic pain exhibited poorer mental health, with mean depression, anxiety, and fatigue scores nearly double that of the non-chronic pain group (PHQ-9: 6.89 vs 3.28, P<0.001; GAD-7: 2.15 vs 1.40, P<0.001; FSS: 21.4 vs 15.4,, P<0.001). Chronic pain was also associated with lower employment rates (34% vs 37%, P<0.001), increased use of medications such as opioids (2.0% vs 0.2%, P<0.001), tricyclic antidepressants (2.4% vs 0.5%, P<0.001), and gabapentinoids (1.6% vs 0.2%, P<0.001), and lower average self-reported sleep duration (7.1 vs 7.23 hours, P<0.001).

Similar patterns were observed among participants included in the longitudinal analysis, with 10,022 (53%) reporting chronic pain at baseline (**Supplementary Table B-3**). Participants included in the longitudinal analysis had a similar age and sex distribution, but had slightly lower FMI scores (3.52 vs 3.67), lower PHQ-9 scores (5.00 vs 5.41), and were more likely to have a university degree (54.1% vs 51.6%) and be employed (38% vs 32%) (**Supplementary Table B-4**).

	Total	No Chronic pain (NP)	Chronic pain (CP)	Difference (CP-NP)	P
	(N=35423)	(N=16654)	(N=18769)		
Sex					
Female	18588 (52 %)	8085 (49 %)	10503 (56 %)	7%	<0.001
Male	16835 (48 %)	8569 (51 %)	8266 (44 %)	0%	
Age (years)					
Mean (SD)	64.5 (7.38)	64.4 (7.43)	64.6 (7.34)	0.2	0.049
Townsend Deprivation Index					
Mean (SD)	-1.90 (2.73)	-1.94 (2.71)	-1.86 (2.75)	0.08	0.006
Marital status					
Married/Partner	26540 (75 %)	12545 (75 %)	13995 (75 %)	0%	0.365
Not married	8746 (25 %)	4057 (24 %)	4689 (25 %)	0%	
Employment status					
Employed	12567 (35 %)	6155 (37 %)	6412 (34 %)	-3%	<0.001
Retired	21544 (61 %)	9975 (60 %)	11569 (62 %)	2%	
Unemployed/Other	1243 (4 %)	494 (3 %)	749 (4 %)	1%	
Missing	69 (0.2%)	30 (0.2%)	39 (0.2%)	0%	
White ethnicity, %	97.5%	97.6%	97.5%	-0.10%	0.911
University Degree, %	52.9%	55.5%	50.6%	-4.90%	<0.001
Current tobacco use, %	2.78%	2.64%	2.90%	0.26%	0.365
Alcohol Use					
Never	2305 (7 %)	1024 (6 %)	1281 (7 %)	1%	<0.001
Rarely	7599 (21 %)	3339 (20 %)	4260 (23 %)	3%	
Weekly	19409 (55 %)	9330 (56 %)	10079 (54 %)	-2%	
Daily	6033 (17 %)	2926 (18 %)	3107 (17 %)	-1%	
Body Mass Index (kg/m2)					
Mean (SD)	26.4 (4.46)	25.9 (4.13)	26.8 (4.70)	0.9	<0.001
Fibromyalgia Index (0-31)					
Mean (SD)	3.59 (3.49)	1.96 (1.93)	5.04 (3.91)	3.08	<0.001
Widespread Pain Index (0-19)					
Mean (SD)	1.27 (1.97)	0.284 (0.764)	2.14 (2.27)	1.86	<0.001
Symptom Severity Scale (0-12)					
Mean (SD)	2.32 (2.09)	1.68 (1.64)	2.89 (2.28)	1.21	<0.001
Sleep duration, hours					
Mean (SD)	7.16 (1.02)	7.23 (0.968)	7.10 (1.06)	-0.13	<0.001
Sleep duration					
<7 hours	8261 (23 %)	3373 (20 %)	4888 (26 %)	6%	<0.001
7-9 hours	24536 (69 %)	12061 (72 %)	12475 (66 %)	-6%	
>9 hours	2480 (7 %)	1163 (7 %)	1317 (7 %)	0%	
Pain intensity, NRS (0-10)					
Mean (SD)	3.70 (2.58)	NA (NA)	3.70 (2.58)	NA	NA
Depression (PHQ-9, 0-27)					

Mean (SD)	5.19 (6.98)	3.28 (5.04)	6.89 (7.96)	3.61	<0.001
Anxiety (GAD-7, 0-21)					
Mean (SD)	1.80 (3.05)	1.40 (2.65)	2.15 (3.32)	0.75	<0.001
Brain fog (SSS)					
Mean (SD)	1.39 (0.575)	1.30 (0.495)	1.47 (0.628)	0.17	<0.001
Fatigue Severity Scale (FSS)					
Mean (SD)	18.6 (13.2)	15.4 (10.7)	21.4 (14.5)	6	<0.001
Doleur Neuropathique 4 (0-7)					
Mean (SD)	1.16 (1.39)	N/A	1.16 (1.39)	NA	NA
Opioid use	1.13%	0.17%	1.99%	1.82%	<0.001
Tricyclic Antidepressant use	1.53%	0.54%	2.42%	1.88%	<0.001
Gabapentinoid use	0.91%	0.19%	1.56%	1.37%	<0.001

Table 3-1. Baseline characteristics of participants included in cross-sectional association between FMI and executive function.

Higher values of Townsend Deprivation Index indicate greater social deprivation. Nociplastic pain assessed using the fibromyalgia index (FMI), with higher scores indicating more severe nociplastic pain. The FMI is the sum of the widespread pain index (WPI) and symptom severity scale (SSS). Pain intensity measured using numeric rating scale (NRS) among participants who indicated they had chronic pain, higher values indicate more severe pain. Depression measured using Patient Health Questionnaire 9-item on the pain questionnaire, with higher scores indicating more severe depression symptoms. Anxiety measured using the General Anxiety Disorder 7-item on the Mental Health and Well-being questionnaire, with higher scores indicating more severe anxiety symptoms. Brain-fog measured using item on subjective cognitive difficulties on SSS, with higher scores indicating more severe brain-fog symptoms. Fatigue measured using the Fatigue Severity Scale (FSS) on the pain questionnaire, with higher scores indicating more severe fatigue symptoms. Note this questionnaire was only offered to participants who reported fatigue on the SSS. Neuropathic pain symptoms measured using the Douleur Neuropathique 4 (DN4) on the pain questionnaire, with higher scores indicating more severe neuropathic symptoms. The difference in values (means, frequencies) for the chronic pain minus the no chronic pain groups are presented. Statistical significance estimated using t-test for continuous variables and Chi-square test for categorical variables. SD, standard deviation.

3.3.3 Confirmatory factor analysis (CFA)

3.3.3.1 Cross-sectional CFA

The cross-sectional CFA model for executive function displayed excellent model fit (CFI 1.0, TLI 1.0, and RMSEA P<0.001; **Figure 3-4**), indicating that the hypothesised factor structure adequately captures the covariance among the observed variables. The matrix pattern recognition test loaded most strongly onto the EF latent factor (standardised loading 0.58), while the TMT and SDS had weaker loadings (0.39 and 0.24, respectively). The residual variances were 0.66 for the matrix test, 0.84 for TMT,

and 0.94 for SDS, reflecting that the latent factor explained a larger proportion of the variance in the matrix pattern test compared to the others, making it a stronger indicator of EF. The weaker loading and higher residual variance for SDS suggests that much of its variance was independent of EF, potentially due to a ceiling effect, as many participants performed near the maximum score. This limited variability may have attenuated its relationship with EF.

At baseline, the chronic pain group scored approximately 3.5 centiles lower than those without chronic pain (median centile 48.46 vs. 51.97) (Aim 1A, **Supplementary Table B-5**).

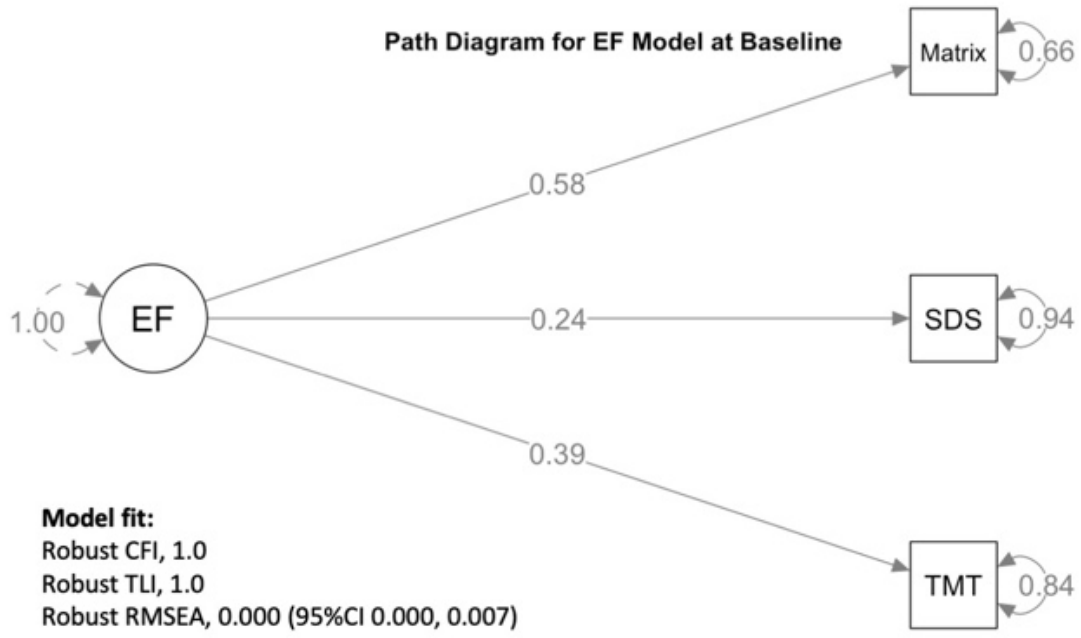


Figure 3-4. Path diagrams for latent variables for executive function at baseline

Standardised loadings and residual variances displayed. Residual variance reflects the proportion of variance in an observed variable unexplained by the latent factor; lower residual variance indicates stronger alignment with the latent construct. EF, executive function. Matrix, matrix pattern recognition test. SDS, digit-symbol substitution test. TMT, trail-making test. CFI, comparative fit index. TLI, Tucker-Lewis index. RMSEA, root mean square error of approximation. 95%CI, 95% confidence interval.

3.3.3.2 Aim 1A&B: Nociplastic pain severity is associated with worse executive function in adults with chronic pain

At baseline, higher FMI scores, a marker of nociplastic pain severity, were associated with worse EF among individuals with chronic pain, but not those without chronic pain (LRT P-interaction <0.001) (**Figure 3-5**). After adjusting for age, sex, and assessment order, each 1-point increase in FMI was associated with a 0.766 centile (95%CI -0.872 to -0.661; P<0.001) lower executive function score. This was modestly attenuated in the fully adjusted model (β -0.488; 95%CI -0.591 to -0.385; P<0.001). These results suggest that higher FMI scores are associated with worse EF, but only in the presence of chronic pain. Detailed results are given in **Supplementary Table B-3** & **Supplementary Table B-4**.

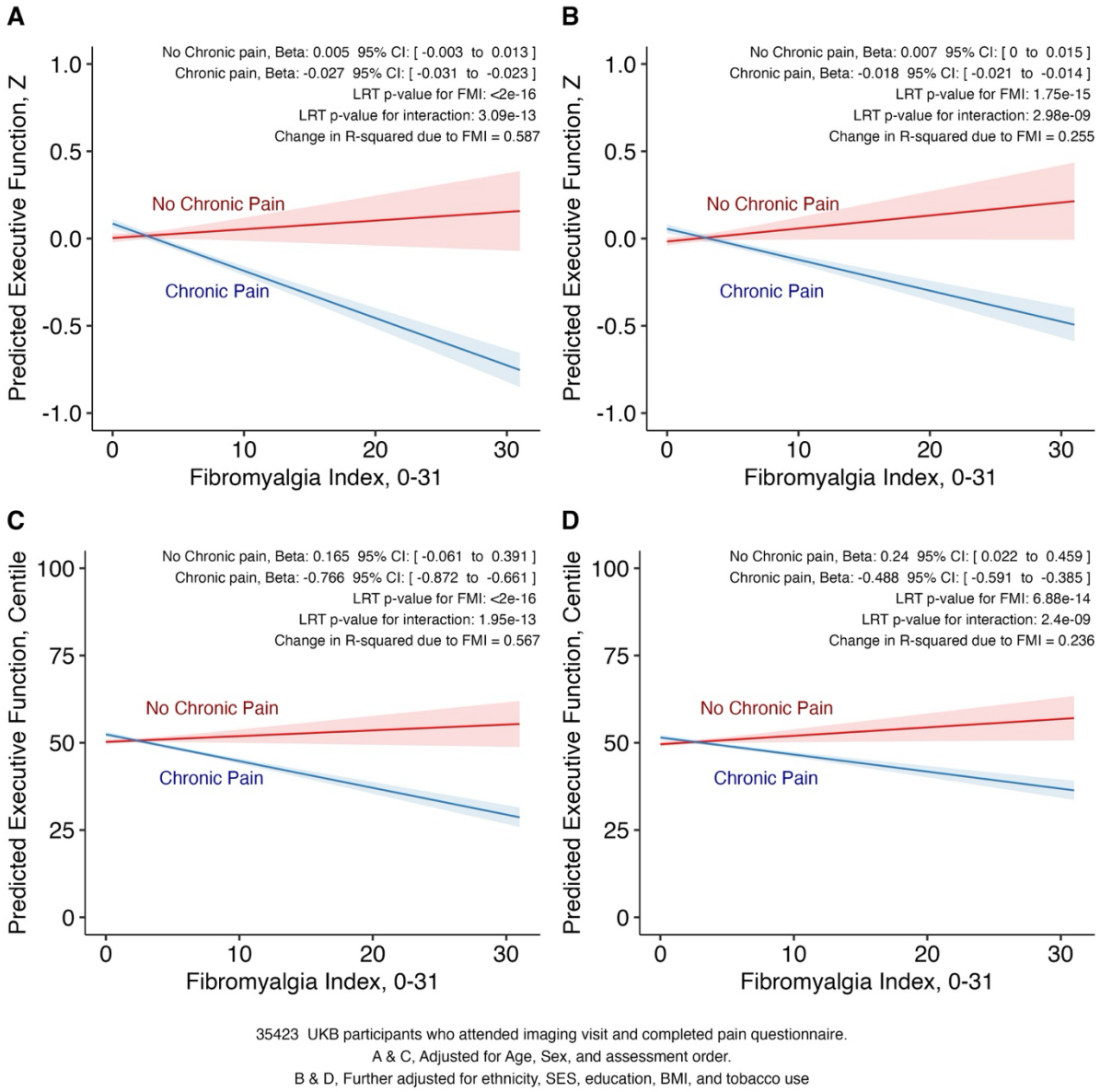


Figure 3-5. Higher Fibromyalgia index (FMI) scores is associated with worse executive function in adults with chronic pain

Panels show the predicted executive function (EF) scores on two scales—standardised (age-adjusted Z-score) in panels A and B, and age-adjusted centile rank in panels C and D—based on the Fibromyalgia Index (FMI) in participants with and without chronic pain. Models in panels A and C are adjusted for age, sex, and assessment order, while models in panels B and D include additional adjustments for ethnicity, socioeconomic status, education, body mass index (BMI), and tobacco use. Shaded regions represent 95% confidence intervals. Chronic pain participants show a stronger negative association between FMI and EF compared to those without chronic pain. The likelihood ratio test (LRT) p-values for interaction indicate a significant difference between groups. This suggests that increasing FMI score is associated with poorer executive function among adults with chronic pain.

3.3.3.3 Association is stronger in males compared to females

Among participants with chronic pain, the relationship between higher FMI score and worse executive function was stronger in males than females (LRT P-interaction <0.001) (

Figure 3-6). After adjusting for age, sex, and assessment order, each 1-point increase in FMI was associated with a 1.071 age-adjusted centile decrease in executive function (95%CI -1.246 to -0.895; P < 0.001) for males, compared to a 0.614 centile decrease (95%CI -0.747 to -0.481; P < 0.001) for females. The association was slightly attenuated in the fully adjusted models (Males: β -0.759; 95%CI -0.929 to -0.588; P<0.001. Females: β -0.364; 95%CI -0.494 to -0.234). Detailed results are given in **Supplementary Table B-5** & **Supplementary Table B-6.**

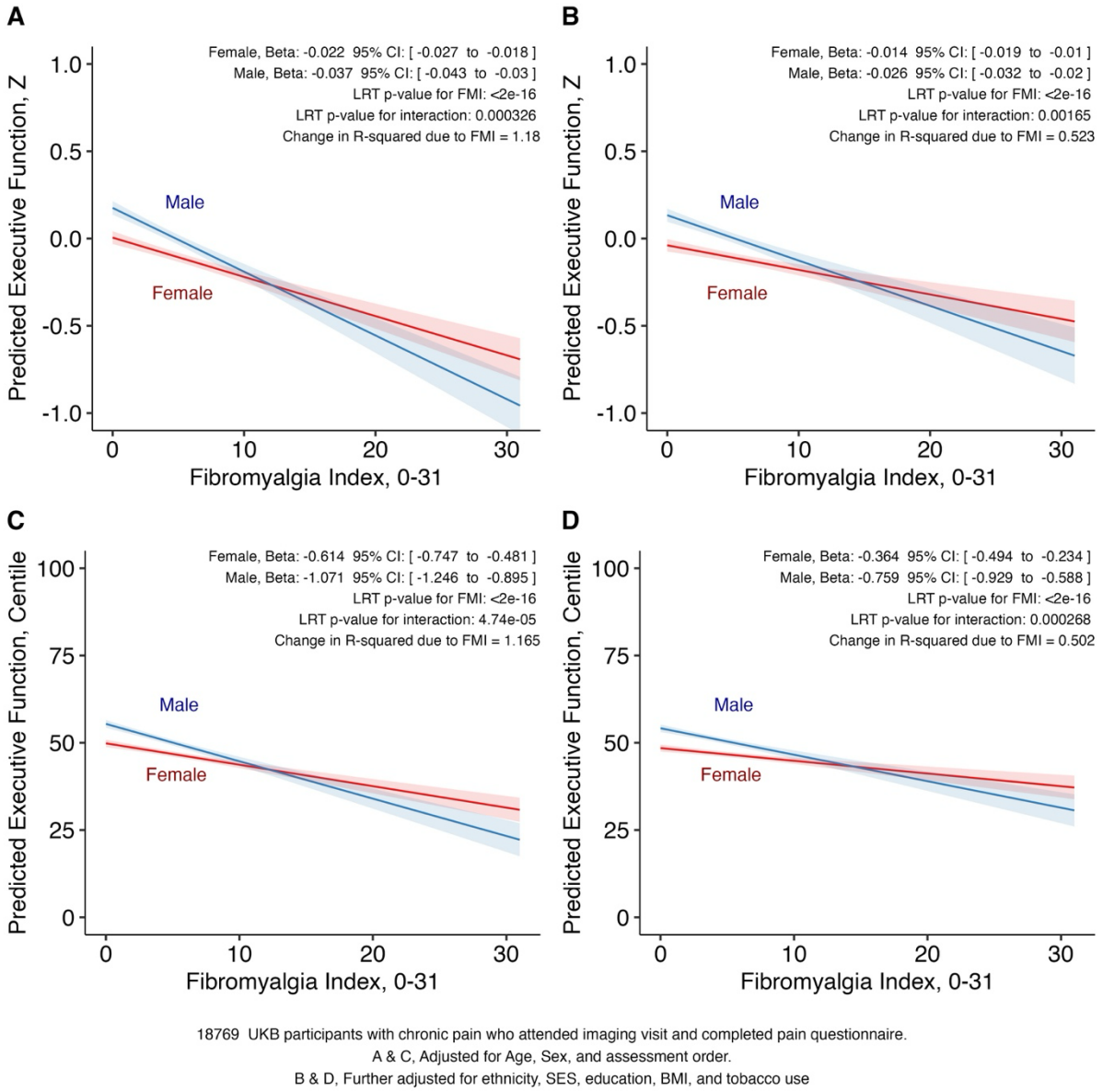


Figure 3-6. Relationship between Fibromyalgia Index (FMI) and executive function (EF) is stronger in males compared to females.

Panels depict predicted EF scores in two formats—standardised (age-adjusted Z-score) in panels A and B, and age-adjusted centile rank in panels C and D—across FMI scores for males and females. Panels A and C adjust for age, sex, and assessment order, while panels B and D include further adjustments for ethnicity, socioeconomic status, education, body mass index (BMI), and tobacco use. Shaded regions represent 95% confidence intervals. A stronger negative association between FMI and EF is evident in males compared to females, as indicated by the interaction P-values from likelihood ratio tests (LRT). These findings suggest that increasing FMI scores are associated with greater reductions in EF, particularly in males with chronic pain.

3.3.3.4 Model diagnostics

Across all models, residuals showed a relatively even spread around zero with no major patterns in residuals vs. fitted plots, indicating adequate linearity. Q-Q plots suggested some deviations from normality, particularly in the tails, which could be attributed to the large sample size amplifying minor non-normality. The scale-location plots showed slight heteroscedasticity in the centile rank-based models, but the variance was reasonably stable across fitted values. Residuals vs leverage plots identified a small number of high-leverage points, yet none exceeded the Cook's distance threshold, indicating no undue influence on model estimates. There was no evidence of multicollinearity, GVIF<2 (Supplementary Table B-10). Given the large sample size, minor deviations from linearity and normality are expected and generally do not impact inference due to the robustness of large-sample statistical properties[400]. Overall, these diagnostics suggest the models are robust and appropriate for inference in a large sample, with any minor violations unlikely to substantially affect results (Supplementary Figure B-1 **to** Supplementary Figure B-8).

3.3.4 Longitudinal CFA

3.3.4.1 Factorial invariance in executive function

To evaluate the stability of executive function measurement over time, CFA was conducted to test factorial invariance across baseline and follow-up assessments (Figure 3-7). The configural model, which allowed item loadings and intercepts to vary, showed a good fit (CFI=0.982, TLI=0.961, RMSEA=0.040, SRMR=0.021), suggesting that the basic EF factor structure was consistent across time points (**Table 3-2**). The

incremental change in model fit indices between the configural, metric, and partial scalar models were within the acceptable range. However, the full scalar model**,** which constrained all intercepts equally across time points, showed poor fit (CFI=0.000, TLI=-0.565, RMSEA=0.249, SRMR=0.149), indicating that full scalar invariance does not hold for EF. Thus, the partial scalar model, where intercepts for the matrix and SDS indicators were constrained to equality, but not for the TMT test, which was permitted to vary, was selected for subsequent analyses.

These findings suggest that the EF measurement properties are relatively stable at the configural, metric, and partial scalar levels, supporting comparisons of factor loadings and partially comparable latent means over time[495], though full invariance was not achieved.

	Parameters (N)	Chi-Square	Df	CFI (robust)	TLI (robust)	RMSEA	SRMR
Configural	20	119.108	7	0.982	0.961	0.040	0.021
Metric	19	127.996	8	0.980	0.963	0.039	0.021
Partial Scalar	18	133.011	9	0.980	0.966	0.037	0.022
Scalar	17	6233.461	10	0.000	-0.565	0.249	0.149

Table 3-2. Model Fit Indices for Factorial Invariance Testing of Executive Function Across Time Points.

Fit indices for the configural, metric, partial scalar, and scalar models assessing factorial invariance of executive function across time points. The configural, metric, and partial scalar models demonstrated acceptable fit, supporting partial invariance (intercept of TMT allowed to vary) of executive function measures over time. However, the scalar model showed poor fit, indicating that full scalar invariance does not hold. Change in CFI or TLI 0.01, RMSEA ≥0.015, and SRMR ≤0.03 between models were considered indicators of factorial invariance. Df, degrees of freedom. CFI, confirmatory factor index. TLI, Tucker Lewis Index. RMSEA, root mean square error of approximation. SRMR, standardised root mean square error residual.

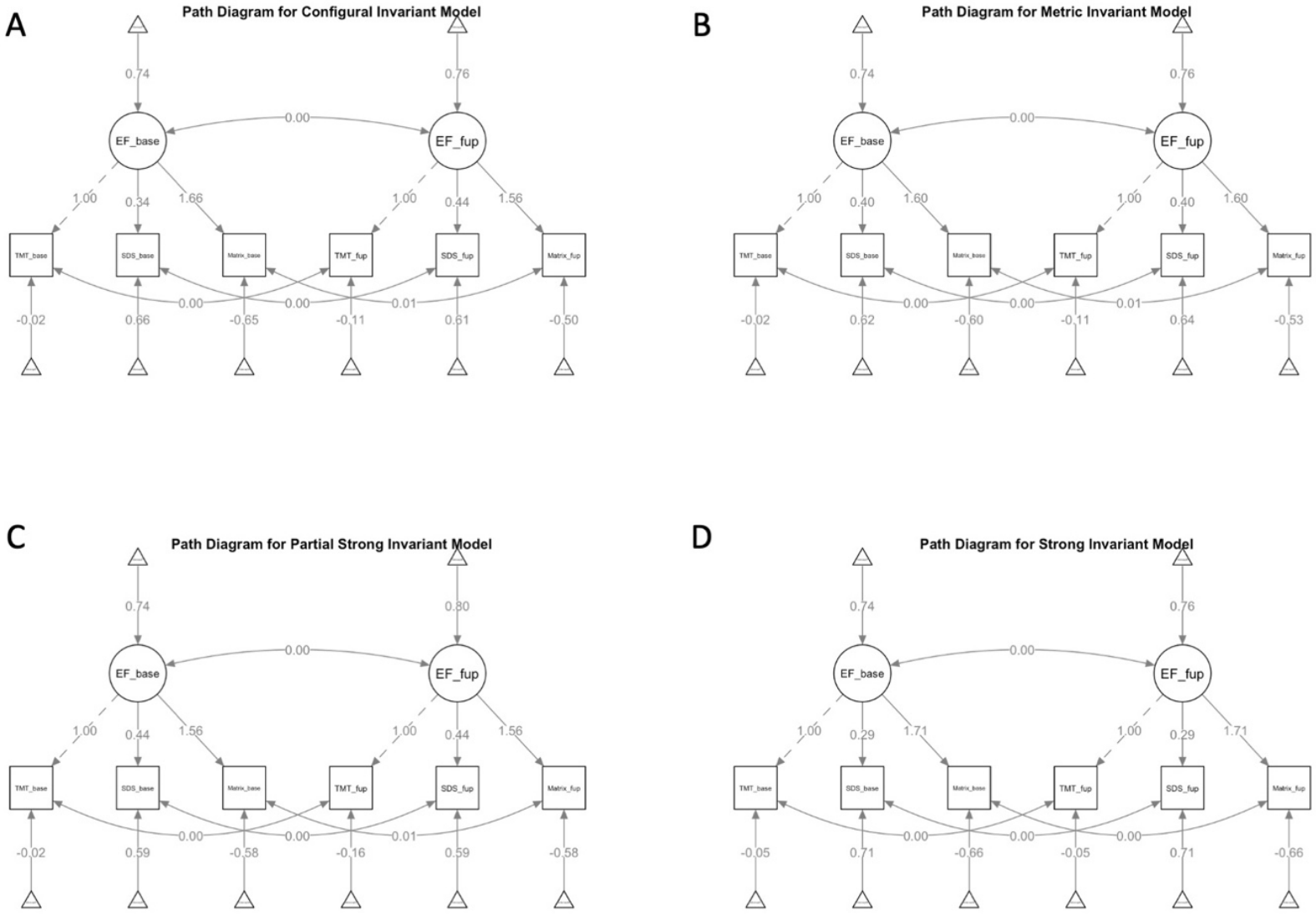


Figure 3-7. Partial scalar invariance exists over time for executive function for UK Biobank participants with chronic time.

Path diagrams illustrate the factorial invariance testing for executive function (EF) across time points (baseline, EF_base; follow-up, EF_fup). Panel A shows the configural invariance model, which establishes the baseline structure. Panel B depicts the metric invariance model, where factor loadings are constrained to be equal across time points. Panel C represents the partial scalar invariance model, with both loadings and intercepts partially constrained (intercept for TMT permitted to vary), indicating partial invariance. Panel D illustrates the strong invariance model, where full scalar invariance is tested. The effects coding method of scaling is used, where the loadings are constrained to equal three, and the intercepts to equal zero. Only partial scalar invariance was achieved, as seen in the fit indices. These findings suggest that while some aspects of the EF construct are stable over time, full scalar invariance does not hold.

3.3.5 Aim 1C: No longitudinal relationship between nociplastic pain severity and executive function

SEM was used to examine the longitudinal relationship between FMI and EF at follow-up, with baseline EF included as a mediator (**Figure 3-8**). In the model adjusted for age and sex (**Panel A**), FMI demonstrated a small negative direct effect on EF at follow-up (β -0.042; 95%CI: -0.074 to -0.01; P=0.011). The indirect pathway through baseline EF was relatively stronger (β -0.141; 95%CI: -0.170 to -0.112; P<0.001), with a total effect of FMI on follow-up EF of β -0.183 (95%CI: -0.217 to -0.149; P<0.001), indicating that higher FMI scores are associated with a greater decline in EF over time. Baseline EF was strongly predictive of follow-up EF (β=0.737, P<0.001), underscoring the stability of EF across time points.

However, in the fully adjusted model (**Panel B**), the small direct effect of FMI on follow-up EF was attenuated and became non-significant (β=-0.021; 95%CI -0.055 to 0.013; P=0.226). The indirect effect through baseline EF was also attenuated, but remained significant (β -0.107; 95%CI -0.140 to -0.074; P<0.001), resulting in a total effect of β -0.128 (95%CI -0.163 to -0.093; P<0.001). Detailed results are provided in **Supplementary Table B-11**. These results indicate that the relationship between FMI and follow-up EF is largely mediated by its relationship with baseline EF, suggesting that nociplastic pain severity is not associated with the rate of cognitive decline.

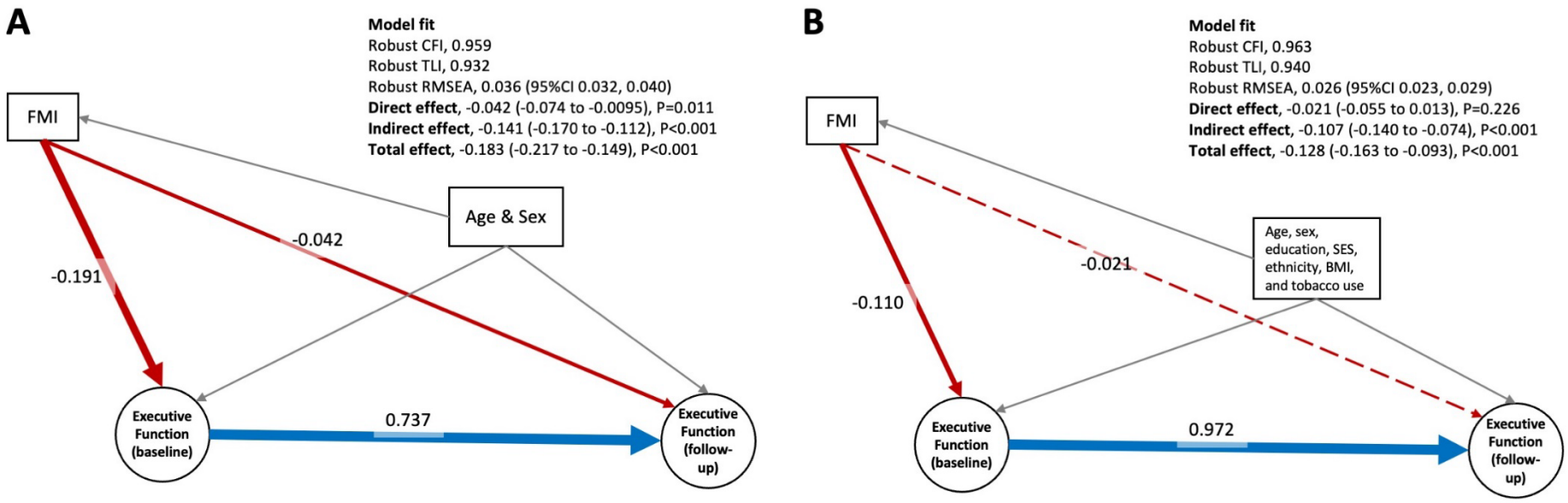


Figure 3-8. No association between fibromyalgia index (FMI) and cognitive decline in UK Biobank.

Structural equation model illustrating the longitudinal relationship between the Fibromyalgia Index (FMI) score and executive function (EF) at follow-up, mediated by baseline EF. Panels A and B represent models adjusted for different sets of covariates. Standardised parameter estimates are displayed, with red lines indicating negative associations and blue lines indicating positive associations. Solid lines represent significant paths, while dashed lines indicate non-significant relationships. Bootstrapped confidence intervals estimated with 5,000 iterations. Panel A includes adjustments for age and sex, while Panel B further adjusts for education, socioeconomic status (SES), ethnicity, body mass index (BMI), and tobacco use. Model fit indices are provided for each panel: CFI, comparative fit index; TLI, Tucker-Lewis Index; RMSEA, root mean square error of approximation.

3.3.6 Aim 2: Mediation analysis

SEM was employed to investigate the longitudinal association between FMI and EF at follow-up, mediated by three distinct sets of pathways outlined in section 3.2.4.4: SPACE symptoms (sleep disturbance, pain, anxiety, cognition, and energy), pain characteristics (pain severity, widespread pain, and neuropathic pain), and analgesia use (opioids, TCAs, and gabapentinoids). Each model included an indirect pathway via baseline EF, and was adjusted for age, sex, education, socioeconomic status, ethnicity, BMI, and tobacco use.

3.3.6.1 Aim 2: Mediation with SPACE symptoms

The SPACE symptom model (**Figure 3-9**) showed a small total effect of FMI on follow-up EF (β=-0.09; 95%CI -0.13 to -0.05; P<0.001), which was almost entirely through an effect on baseline EF (β=-0.06; 95%CI -0.11 to -0.02; P=0.0015), indicating that the influence of FMI on EF at follow-up operates largely through its effect on prior EF. Although FMI was strongly associated with all SPACE symptoms, there were no significant indirect pathways from FMI to EF at follow-up *via* the SPACE symptoms (P>0.05 for all). This suggests that there is no longitudinal effect of FMI on EF mediated by the SPACE symptoms. Detailed results are given in **Supplementary Table B-12**.

At baseline, however, FMI was associated with worse baseline EF through indirect pathways involving abnormal short/long sleep duration (β=-0.013; 95%CI -0.02 to -0.01; P<0.001), pain severity (β=-0.03 95%CI -0.04 to -0.02; P<0.001), and anxiety (β=-0.03; 95%CI -0.04 to -0.02; P<0.001). Interestingly, there was an indirect pathway *via* depression and *better* baseline EF (β=0.04; 95%CI 0.01 to 0.07; P=0.003), which

warrants further investigation. This may reflect compensatory mechanisms, differential symptom impacts, or other unmeasured factors. Pathways *via* brain-fog and fatigue were close to zero and not significant, suggesting limited mediating roles for these characteristics. These results suggest that while the impact of FMI on EF at baseline is partially mediated by symptoms such as abnormal sleep duration, pain severity, and anxiety, its effect on follow-up EF is primarily driven by its influence on baseline EF rather than direct or mediated by SPACE symptoms.

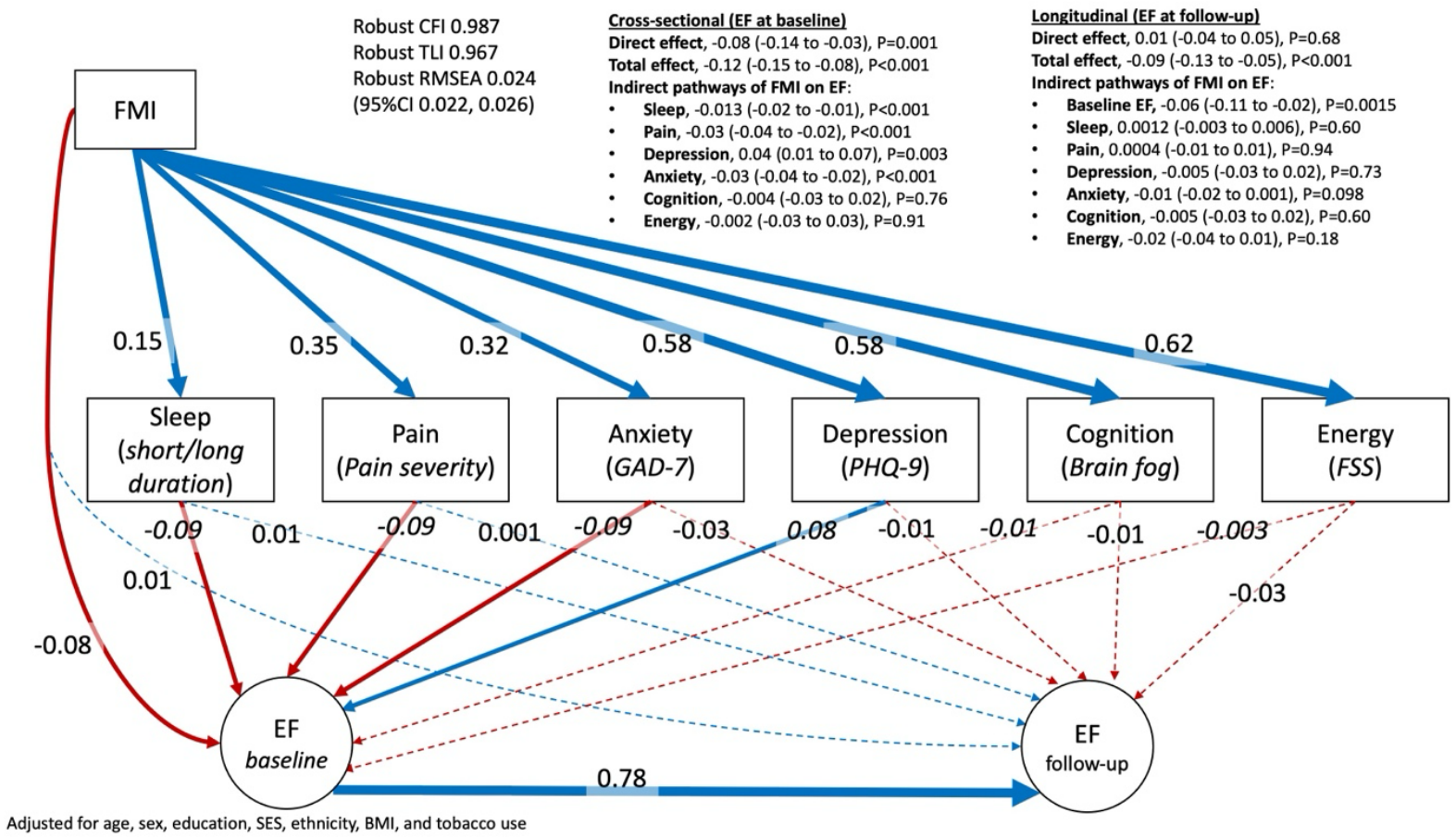


Figure 3-9. Sleep duration, pain intensity, and anxiety partially mediate cross-sectional relationship between fibromyalgia index (FMI) and baseline executive function (EF).

Structural equation model of the longitudinal effect of FMI on baseline and follow-up executive function (EF) via SPACE symptoms. Standardised parameter estimates are presented, with blue lines indicating positive associations and red lines indicating negative associations. Solid lines represent significant paths, while dashed lines denote non-significant relationships. Bootstrapped confidence intervals estimated with 5,000 iterations. The model adjusts for age, sex, education, SES, ethnicity, BMI, and tobacco use. CFI: Comparative Fit Index; TLI: Tucker-Lewis Index; RMSEA: Root Mean Square Error of Approximation.

3.3.6.2 Aim 2B: Mediation with Pain characteristics

Similarly, there were no significant indirect pathways between FMI and EF at follow-up *via* pain characteristics (**Figure 3-10**). However, at baseline the association between FMI and worse baseline EF was partially mediated through pain severity (β=-0.03; 95%CI -0.04 to -0.01; P<0.001), and neuropathic pain (β=-0.03; 95%CI -0.05 to -0.02; P<0.001). Together, these account for approximately half of the total effect of FMI on baseline EF. Counterintuitively, there was an indirect pathway *via* widespread pain and *better* baseline EF (β=0.07; 95%CI 0.01 to 0.13; P=0.017), which also warrants further investigation. Detailed results are given in **Supplementary Table B-13.**

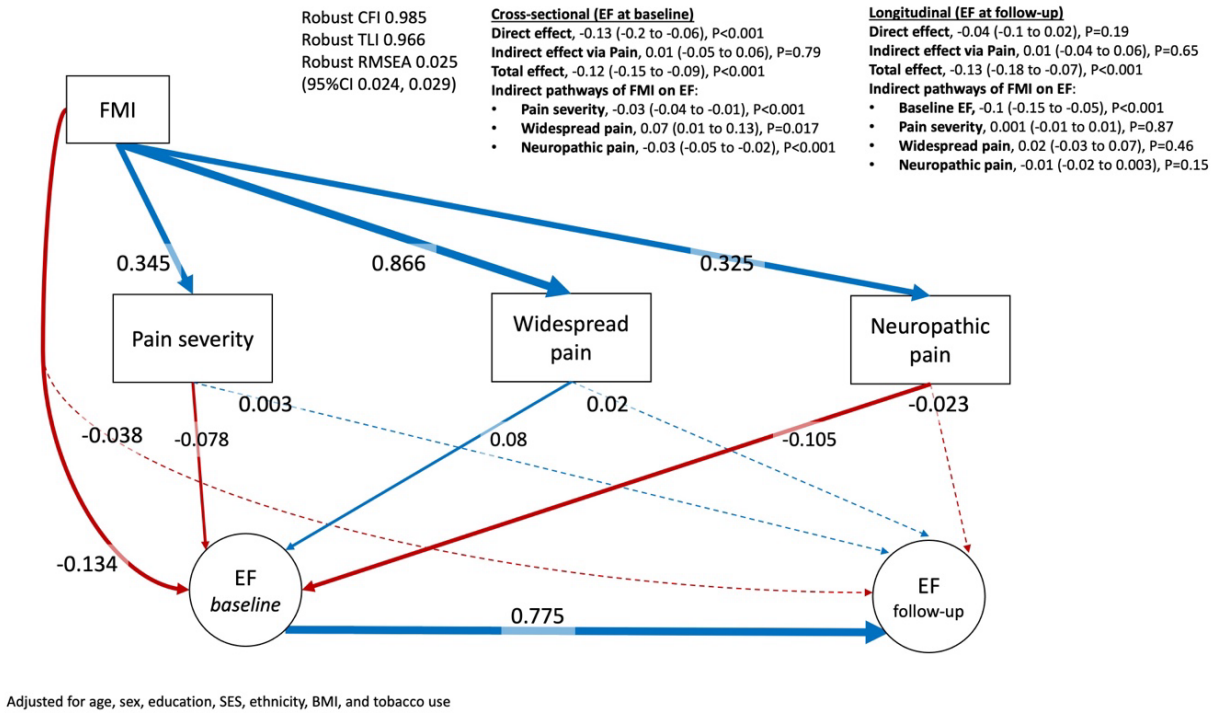


Figure 3-10. Pain intensity and neuropathic pain symptoms partially mediate cross-sectional relationship between fibromyalgia index (FMI) and baseline executive function (EF).

Structural equation model of the longitudinal effect of FMI on baseline and follow-up EF via pain characteristics. Standardised parameter estimates are presented, with blue lines indicating positive associations and red lines indicating negative associations. Solid lines represent significant paths, while dashed lines denote non-significant relationships. Bootstrapped confidence intervals estimated with 5,000 iterations. The model adjusts for age, sex, education, SES, ethnicity, BMI, and tobacco use. CFI: Comparative Fit Index; TLI: Tucker-Lewis Index; RMSEA: Root Mean Square Error of Approximation.

3.3.6.3 Aim 2C: Mediation with analgesia use

Finally, there were also no significant indirect pathways between FMI and follow-up EF *via* analgesia use (**Figure 3-11**). There was a small, marginally significant, indirect effect on baseline EF *via* analgesia use (β=-0.008; 95%CI -0.016 to -0.0009; P=0.029), which accounted for 7.04% of the total effect. This was primary through TCA use, through which the indirect effect was also marginally significant, albeit very small (β=-0.004; 95%CI -0.008 to -0.0001; P=0.044). Detailed results are given in **Supplementary Table B-14.**

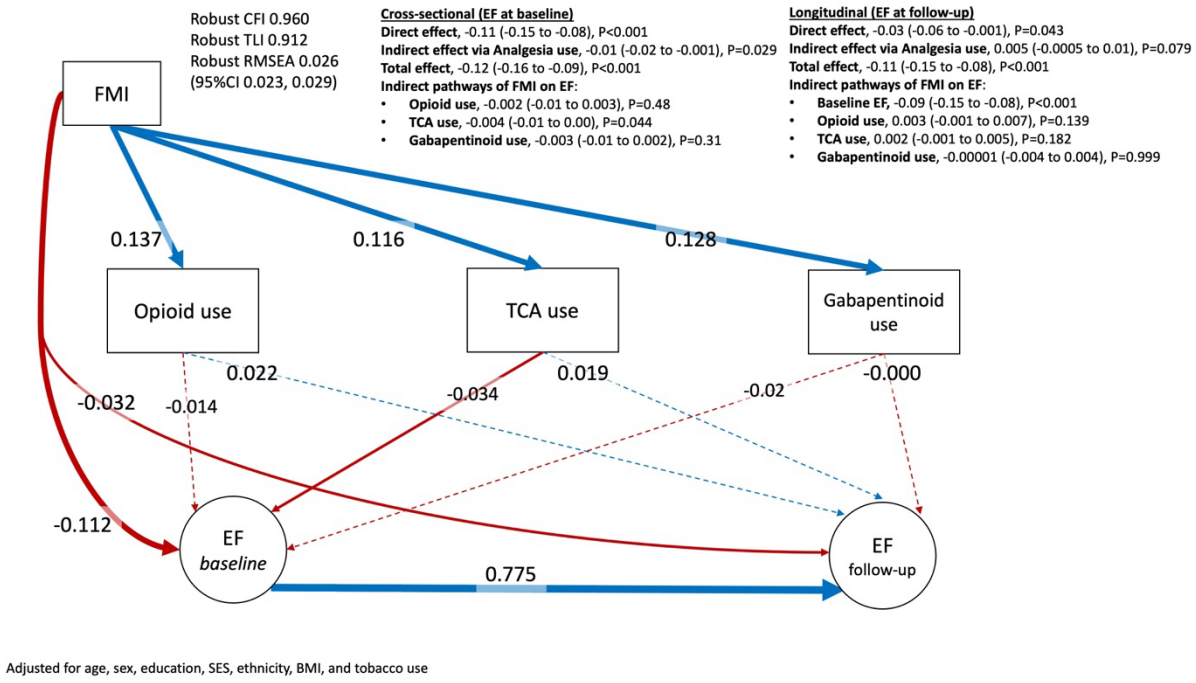


Figure 3-11. Analgesia use does not mediate cross-sectional relationship between fibromyalgia index (FMI) and baseline executive function (EF).

Structural equation model depicting the indirect effects of FMI on baseline and follow-up EF through analgesia use. Blue and red lines represent positive and negative associations, respectively, with solid lines showing significant relationships and dashed lines for non-significant paths. Bootstrapped confidence intervals estimated with 5,000 iterations. Adjusted for covariates such as age, sex, education, SES, ethnicity, BMI, and tobacco use. TCA, tricyclic antidepressant. CFI: Comparative Fit Index; TLI: Tucker-Lewis Index; RMSEA: Root Mean Square Error of Approximation.

3.3.6.4 Sensitivity analyses

Higher FMI scores were associated with worse cognitive performance on all three tasks. Sensitivity analyses showed that the timing of assessments, including the COVID-19 period, did not affect these results. Full details are in **Appendix B.7**.

3.4 Discussion

3.4.1 Key message

This study adds to existing literature by demonstrating that severity of nociplastic pain was not associated with a significant decline in executive function over a 3-year period in a large sample of middle-age British adults (**Figure 3-8**). However, at baseline, adults with chronic pain had 3.5 centile lower executive function compared to those with no chronic pain, and among those with chronic pain, more severe nociplastic pain severity was associated with worse executive function, with each 1-point increase in the FMI score associated with a 0.49 centile decrease in executive function (**Figure 3-5**). This cross-sectional association was almost twice as strong in males compared to females, and was partially accounted for by abnormal sleep duration, anxiety, pain severity and neuropathic pain features, but not by depressive symptoms, fatigue or analgesia use (**Figure 3-9, Figure 3-9, Figure 3-10**).

3.4.2 Existing literature

Over half (53%) of participants reported chronic pain, aligning with prevalence estimates from the UK and internationally[288]. As outlined in Chapter 1, evidence for an association between chronic pain on cognitive decline is mixed (**Table 1-1**). Studies of the Health and Retirement Study cohort found that both presence[492] of chronic pain and persistence[36] of pain interference are associated with cognitive impairment in older adults[36]. Similarly, pain interference is associated with cognitive impairment in the Einstein Ageing Cohort[147] and Elderly in Boston[463; 464] cohorts. Two recent

studies of UK Biobank also found an association between multi-site chronic pain and elevated dementia risk[448; 522]. However, there are relatively fewer studies of the longitudinal association of chronic pain and executive function, which may be a relevant, and sensitive, marker of cognitive abilities in a group of middle-aged adults.

While a recent study of older adults in the PAQUID cohort linked chronic pain with poor cognitive task performance[385], the English Longitudinal Study of Ageing (ELSA) found no such association[470]. Unlike these studies, the present study used the fibromyalgia index (FMI) score, a clinically relevant pain phenotype linked to nociplastic pain severity[159]. This pain type, characterised by widespread pain and hypersensitivity due to dysfunctional pain pathways, often includes cognitive symptoms.

In addition, in this study I evaluated a latent variable reflecting underlying executive function using cognitive tasks from UK Biobank. This general factor for executive function reduces measurement error and summarises multiple tasks into a single measure, enabling detection of subtle cognitive variations missed by individual tests, particularly those designed to detect severe cognitive disorders like dementia[151]. Furthermore, I evaluated the longitudinal stability of this latent factor and controlled for age at assessment, ensuring that observed effects were not confounded by age-related cognitive decline or changes in measurement properties over time. While a recent study by Zhao et al. also found a cross-sectional link between multi-site chronic pain and age-related cognitive task performance in UK Biobank, they did not examine nociplastic pain severity, or longitudinal cognition changes across time points[522].

3.4.2.1 *Sex differences*

Despite the fact that females are more susceptible to nociplastic pain, males exhibited a relationship between nociplastic pain severity and executive function which was almost twice as strong as in females, a novel finding in humans (
Figure 3-6). This finding aligns with preclinical evidence suggesting that males may exhibit greater susceptibility to pain-induced cognitive impairments. For example, in animal models of neuropathic pain, male rodents show pronounced deficits in prefrontal cortex-dependent tasks, potentially due to maladaptive plasticity in prefrontal networks[412]. In contrast, female rats display earlier and heightened nociceptive responses but recover more quickly from associated cognitive and emotional impairments[222]. These differences may be driven by sex-specific neural and hormonal mechanisms. For instance, in humans, males exhibit stronger pain-induced connectivity between the PAG and amygdala, which is implicated in emotional and cognitive processing[268]. Thus, even though nociplastic pain is less prevalent in males, they may be more vulnerable to its cognitive-affective effects.

3.4.2.2 Mediation analysis

In this study, I conducted mediation analyses to explore the relationship between FMI scores, executive function, and potential mediators: the SPACE cluster, pain characteristics, and analgesia use. My findings show that FMI was associated with poorer executive function cross-sectionally but not with a significant acceleration decline in executive function over time. The association between FMI and executive function at follow-up was largely via an effect on baseline executive function. In turn, a

modest proportion of the cross-sectional association between FMI and baseline executive function was through indirect pathways via abnormal sleep duration, anxiety, pain severity and neuropathic symptoms. These may represent potential therapeutic targets, such as improving sleep, treating pain, or addressing anxiety.

3.4.2.2.1 Sleep

Sleep impairment is a potential mechanism through which chronic pain is associated with worse cognition[115]. Previous work in UK Biobank and other cohorts has found a U-shaped relationship between sleep duration and cognitive performance[281; 442; 496; 510]. Sufficient restorative sleep is required for memory consolidation, and executive functions such as attention[226; 290]. Long sleep duration may reflect disrupted sleep architecture, suggesting non-restorative sleep[33], which is common in chronic pain[53]. In fibromyalgia, levels of sleep impairment correlate with cognitive impairment[489]. A potential explanation for the similarity of the cognitive dysfunction seen in pain disorders and insomnia disorder is the *hyper-arousal theory* of insomnia[368]. This posits that there is an impaired ability to modulate brain activity according to cognitive demands in insomnia, with increased activation of resting-state networks, such as the default mode network (DMN), at rest. Similarly, patients with fibromyalgia report increased sensitivity to external stimuli, such as noise and smells, and greater susceptibility to distractions[245]. This also suggests an inability to focus brain activity according to cognitive demands and may account for the subjective and objective cognitive dysfunction seen in fibromyalgia. Thus, improving sleep may improve executive function in nociplastic pain disorders such as fibromyalgia.

3.4.2.2.2 Pain characteristics

Pain severity and neuropathic pain features displayed significant, albeit modest, indirect pathways with baseline executive function, perhaps due to pain's impact on cognitive resources and attention. Pain can monopolise attention and disrupt cognitive resources, particularly if it is intense and persistent[404]. Studies in healthy adults indicate that high-intensity pain has an interruptive effect on cognitive performance, particularly during tasks requiring cognitive flexibility, such as task-switching, a component of executive function[468]. However, there may be a bidirectional relationship between pain intensity and task difficulty; cognitive tasks of low-to-medium complexity may themselves distract individuals from pain, while performance on more challenging cognitive tasks are disrupted by the presence of high-intensity pain[266; 325]. This suggests that there is a threshold for pain intensity and task difficulty where pain shifts from being distractable to having a distracting effect itself.

Compared to nociplastic pain conditions like fibromyalgia, there is less literature examining cognitive function in neuropathic pain conditions. Patients with neuropathic radicular pain display impaired performance on executive function tasks compared to healthy controls[327]. Furthermore, when comparing patients with neuropathic pain to those with fibromyalgia, neuropathic pain patients performed worse on tasks requiring sustained attention[215]. However, fibromyalgia patients report similar sensory symptoms to patients with neuropathic pain, suggesting there may be overlap in clinical profiles[244]. Neuropathic pain measures, such as the PainDETECT

questionnaire, may capture more centrally-mediated pain which may be associated with worse cognitive function.

This study also found that the widespreadness of pain was not associated with worse executive function. In fact, paradoxically, after controlling for pain severity and neuropathic features, widespreadness had a small positive association with executive function. This contrasts with previous studies which show that chronic widespread pain – a key clinical feature of fibromyalgia – is associated with worse performance on a digit symbol substitution test[261]. However, no studies have previously assessed the concurrent impact of pain intensity, widespreadness, and other characteristics on cognition. It might be that widespreadness is a marker of severity, but it is the intensity of pain and neuropathic-like features, rather than pain distribution, which impact cognitive function.

3.4.2.2.3 Anxiety & depression

Anxiety symptoms also displayed a small indirect association with baseline executive function. Anxiety, in particular apprehensiveness or worry, is associated with impaired cognitive flexibility, resulting in difficulties shifting attention or adapting to new information[483]. Anxious arousal – or panic – affects executive functions more generally, with impacts on inhibition and working memory[407; 411]. However, there is also a bidirectional relationship between anxiety and cognitive function; impaired executive function may itself contribute to anxiety by impacting the ability to shift attention away from threatening stimuli[517]. People with chronic pain disorders, such

as fibromyalgia, have a high co-occurrence of anxiety disorders[303]. Anxiety and pain conditions both display greater activation of similar brain regions, such as the amygdala and ACC, suggesting there may be shared pathways for pain perception and anxiety[523]. The presence of anxiety can reinforce chronic pain in a vicious feedback loop; chronic pain can increase anxiety, where fear of pain and anxiety increase pain sensitivity[20]. Patients with high levels of anxiety show worsening of pain and greater disability over time[265].

In contrast, there was no observed indirect effect with executive function via depressive symptoms. Chronic pain and depression share a bidirectional link, potentially affecting pain perception through mood-influenced brain activity[45]. Depression is often associated with pain, and can impair cognitive function in individuals with or without pain. Despite its role as a mediator in pain-cognition relationships in arthritis patients[64; 212], depressive symptoms did not mediate the pain-cognition association here. This may be because this study accounted for multiple possible indirect effects concurrently, which were not accounted for in previous studies.

3.4.2.2.4 Brain-fog & fatigue

Although fibromyalgia patients often report subjective cognitive difficulties ("brain-fog") and fatigue, and prior studies have linked these symptoms to objective cognitive performance[245], neither factor mediated the relationship between pain and executive function in this study. One possible explanation is that brain-fog may reflect a more generalised perception of cognitive challenges rather than specific impairments in executive function. Additionally, fatigue, while pervasive in fibromyalgia, may exert a

more global impact on energy levels and task persistence rather than directly impairing executive processes.

Research in fibromyalgia and other chronic pain conditions suggests that fatigue depletes cognitive resources, possibly impairing executive functions[23]. This effect may stem from reduced motivation for demanding tasks, where the effort required outweighs the perceived rewards[461]. This impact appears to be synergistic with pain severity, becoming pronounced with greater pain[445]. However, these effects might predominantly influence subjective cognitive effort rather than objective executive deficits[118], which may account for the lack of observed indirect effect on objective executive function via fatigue in this study.

Another contributing factor may be the moderating role of anxiety; individuals with greater anxiety symptoms may have a heightened awareness of their cognitive difficulties, aligning their subjective perceptions more closely with actual cognitive impairments[24]. The indirect pathway through anxiety observed here suggests that anxiety may be a stronger driver of the pain-cognition relationship, potentially overshadowing the contribution of brain-fog and fatigue.

3.4.2.2.5 Analgesia use

Analgesia medications, especially opioids, have been suggested as a link between chronic pain and poor cognition, although the evidence is conflicting[234; 351]. This study did not find that opioid use mediated an association with executive function, which aligns with a recent systematic review which found that there was no worsening of cognition associated with opioid use in chronic non-cancer pain[351]. However, this

study relied on self-reported use, which may be susceptible to recall bias[487]. Furthermore, I was unable to consider duration or dose of opioid use, which may also be relevant. However, studies comparing self-reported analgesia use with prescription records have found generally good concordance[119; 255]. Other explanations include confounding by indication; for example, physicians may be less likely to prescribe opioids to patients at risk of adverse cognitive outcomes. However, together with existing literature on the topic, the present study suggests that use of analgesics, such as opioids, are unlikely to be an important factor in executive dysfunction associated with nociplastic pain.

3.4.2.3 Strengths & limitations

The key strengths of this study are the examination of nociplastic pain severity with the FMI score, large sample size, longitudinal design, inclusion of a broad range of confounders and mediators, and examination of a latent construct for executive function longitudinally, thus ensuring observed effects were due to changes in the latent construct rather than due to changes in test characteristics over time, as well as reducing measurement error.

This study is limited by the inclusion of two time-points and relatively short follow-up; thus reverse causation cannot be excluded. Cognition may affect pain reporting[354], or future development or persistence of pain. However, cognitive disorders, such as dementia, may be associated with reduced pain reporting[52], which may be expected to bias this association towards the null. Similarly, there are limitations to cross-

sectional mediation analysis. Several of the mediators, such as anxiety, may be affected by executive function abilities.

Residual confounding may also account for some of the association observed. Although I adjusted for socio-demographic and lifestyle factors, these may have been incompletely accounted for, and there may be other factors, such as adverse childhood events, which were not included in the analysis. Furthermore, relative timing of the pain and cognitive assessments to each other did not affect the results. Similarly, timing in relation to the COVID-19 pandemic, which may affect cognition[521], also did not alter the results. Measurement error may impact on the findings, as information on pain, mediators and covariables were self-reported. This is a particularly relevant limitation for the analysis of sleep duration and analgesia use. Self-reported sleep duration is often different from observed sleep duration using actigraphy or PSG, and the magnitude of this difference varies between individuals with factors such as mood[293]. It also was not possible to differentiate daytime naps from nighttime sleep, for example; napping can have both beneficial and harmful effects on cognition depending on the context[154]. In addition, UK Biobank may suffer from a healthy volunteer bias, limiting generalisability[441]. Selection bias is also an issue in this study due to the relatively low response rates to the follow-up pain and cognitive assessments in UK Biobank.

3.4.3 Conclusion

In summary, although nociplastic pain severity is associated with worse executive function in adults with chronic pain, reassuringly it is not associated with a faster rate of

cognitive decline. Sleep disturbance, anxiety symptoms, and pain severity represent promising therapeutic targets to improve executive function in nociplastic pain.

These findings underscore the importance of adequate pain management and addressing sleep disturbance and anxiety to potentially mitigate cognitive difficulties in individuals with chronic pain. Moreover, the finding that males are more susceptible to the deleterious effects of pain on executive function warrants further exploration. Understanding the mechanisms for the cognitive dysfunction observed in chronic pain will allow the identification of interventions to improve cognition in this population. Further studies evaluating the temporal association between chronic pain and cognition over longer time periods, in addition to changes in brain structure and function on neuroimaging, and effect of treatment for pain on cognitive outcomes, are necessary to shed light on the nature of the relationship between chronic pain and cognition.

4 Chapter Four: Relationship between DPMS connectivity and nociplastic pain severity in UK Biobank

4.1 Introduction

Nociplastic pain, typified by conditions such as fibromyalgia, arises from altered nociceptive processing in the central nervous system rather than clear peripheral or somatosensory pathology[365]. This pain phenotype typifies the complex interplay between sensory, emotional, and cognitive dimensions of chronic pain[230]. The Fibromyalgia Index (FMI) serves as a valuable composite marker for nociplastic pain severity, capturing its multidimensional nature[502].

The descending pain modulatory system (DPMS) regulates nociceptive input through its dual capacity to facilitate and inhibit pain signals[27; 197]. However, the structural and functional connectivity within the DPMS in relation to nociplastic pain remains poorly understood, particularly at a population level.

At its core, the DPMS comprises the periaqueductal grey (PAG) and rostral ventromedial medulla (RVM), which integrate ascending nociceptive and descending cortical inputs and modulate nociceptive transmission at the spinal level[197; 243]. The PAG and RVM operate within a broader network involving the hypothalamus, amygdala, anterior cingulate cortex (ACC), and dorsolateral prefrontal cortex (dlPFC).

The RVM directly modulates nociceptive input from the spinal cord and descending control from higher centres through two classes of neurons ("ON-cells" and "OFF-cells") that mediate pain facilitation and inhibition, respectively[27; 82]. The PAG integrates top-down cortical inputs with bottom-up nociceptive signals, coordinating autonomic and defensive responses to pain. Altered PAG connectivity has been observed in chronic pain conditions, including fibromyalgia[190; 311; 334]. The hypothalamus plays a role in the autonomic and stress-related responses to pain and is anatomically and functionally connected to the PAG[188]. It is implicated in the regulation of descending inhibitory pathways and the affective components of pain[207]. The amygdala serves as an important interface between the DPMS and the emotional dimensions of pain. It modulates affective pain processing, fear responses, and the regulation of stress-related pain pathways[221].

Cortical regions also play key roles in DPMS function. The rostral ACC (rACC) supports descending pain inhibition and the modulation of affective pain responses[475], with reduced connectivity linked to impaired conditioned pain modulation and chronic pain vulnerability[220]. The subgenual ACC (sgACC) integrates emotional and autonomic responses to pain, and dysfunction in this region is associated with chronic pain and emotional dysregulation in chronic[67]. Finally, the dlPFC plays a role in the cognitive control of pain, including attentional modulation and pain distraction mechanisms, with reduced activity and connectivity contributing to impaired executive function and emotional regulation in chronic pain[346].

4.1.1 Aims & objectives:

This study utilises the UK Biobank's neuroimaging and behavioural data to investigate the functional and structural connectivity of the DPMS at a population-level. By integrating multimodal imaging with measures of nociplastic pain severity, biopsychosocial factors relevant to chronic pain, and executive function, it aims to elucidate the neural mechanisms underlying nociplastic pain and its cognitive and emotional dimensions, with implications for disorders like fibromyalgia.

Primary objective:

1) To investigate the relationship between DPMS connectivity (functional and structural) and nociplastic pain severity at a population-level.

Secondary objectives:

2) To identify the DPMS nodes and pathways most strongly associated with nociplastic pain severity.
3) To evaluate if DPMS connectivity mediates the relationship between nociplastic pain severity and executive function.
4) To explore how DPMS connectivity interacts with biopsychosocial characteristics relevant to nociplastic pain.

4.2 Methods

4.2.1 Study population

This is a cross-sectional study of participants in UK Biobank. An overview of UK Biobank has been outlined earlier in Chapter 3 (Section 3.2.1). UK Biobank plans to image 100,000 participants across four centres: Stockport (opened April 2014), Newcastle-upon-Tyne (April 2017), Reading (June 2018), and Bristol (February 2020). Initially, email invitations to approximately 330,000 participants were sent, with postal invitations to all participants subsequently mailed in 2020. Fewer than 0.5% of participants, including those who left the UK or opted out, were not invited[273].

This study included participants who attended the neuroimaging visit between 2014-2023, and who also completed an online Pain Questionnaire in 2019 (**Figure 4-1**). There was a pause in neuroimaging from the onset of the COVID-19 pandemic between March 2020 and February 2021. As previously described, I excluded a small number of participants with dementia or a serious neurological condition which may affect pain reporting. The present study was approved as UK Biobank application number 45465.

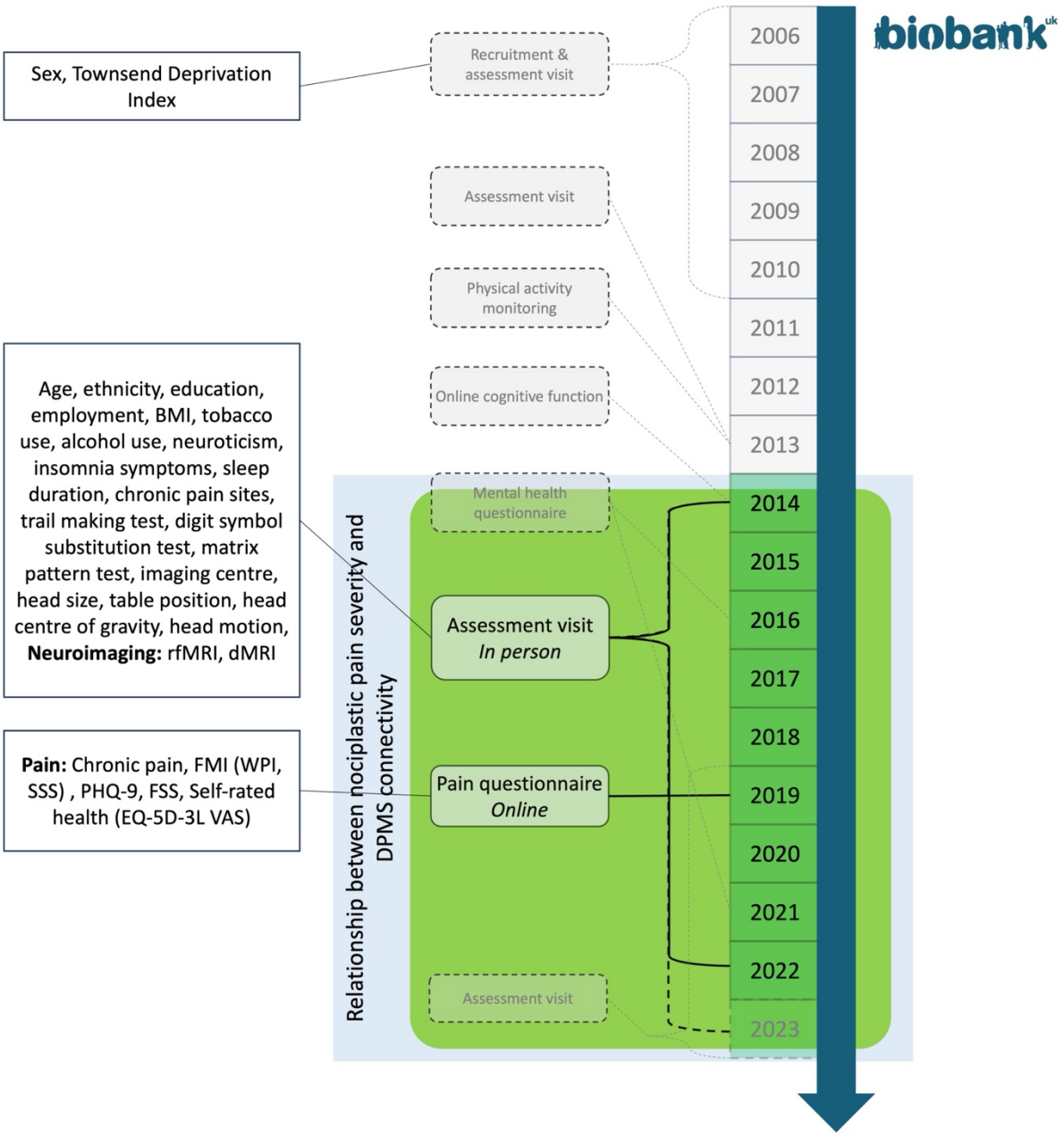


Figure 4-1. Flow diagram of the timeline for the main assessments in UK Biobank.

The assessments used in the current study are highlighted in green. All participants for whom UK Biobank has a current email address (N= ~333,000) were invited to attend follow-up visits and complete online questionnaires. Commencing 2020, UK Biobank also began sending postal invitations for imaging, in addition to email invitations. A small number (<0.5%) of participants have withdrawn or moved outside the UK. Functional connectivity (rs-fMRI) data were extracted for participants scanned between May 2014 and June 2023 (N= 60,404)), while structural connectivity (dMRI) data were extracted for a subset of 33,143 participants scanned between August 2014 and April 2022. The smaller dMRI cohort reflects an earlier data extraction to reduce computational intensity, focusing only on participants who completed the Pain Questionnaire. An expanded battery of cognitive assessments was introduced in imaging visits conducted after December 2016, and participants who attended the imaging visit prior to this were not included in the mediation analysis with executive function. Sex and Townsend deprivation index were only assessed at recruitment. BMI, body mass index. rfMRI, resting state MRI. dMRI, diffusion-weighted MRI. NRS, numeric rating scale. FMI, fibromyalgia index. PHQ-9, patient health questionnaire 9-item. FSS, fatigue severity scale. EQ-5D-5L, EuroQoL 5-Dimensions 5-Level. VAS, visual analogue scale.

4.2.2 Data preparation

I used the fibromyalgia index (FMI) score as a measure of nociplastic severity to find any associations between functional (using resting state imaging) and structural (using diffusion-weighted imaging) connectivity patterns between key nodes in the DPMS (Objectives 1&2, Section 4.2.3). I repeated this analysis after stratifying the sample into those with and without chronic pain (Objectives 1&2, Section 4.2.3.2). I then used structural equation modelling (SEM) to assess whether DPMS connectivity mediates the cross-sectional relationship between FMI and executive function in chronic pain (Objective 3, Section 4.2.4). These were all adjusted for both imaging and non-imaging confounds. Finally I used canonical correlation analysis (CCA) to provide insights into how DPMS connectivity relates to behavioural characteristics in chronic pain (Objective 4, Section 4.2.5).

4.2.2.1 Behavioural data

A detailed description of the cleaning and preparation of behavioural data was outlined in Chapter 3 (Section 3.2.3). As with the previous study, nociplastic pain severity was measured using the FMI[499]. A latent factor for executive function was constructed using three cognitive tasks performed at the imaging visit, the Trail Making Test, Digit-Symbol Substitution, and Matrix Pattern Recognition, using methods described in chapter 3 (Section 3.2.3.2 & Section 3.2.4.1). Socio-demographic and lifestyle confounds were selected *a priori*[230], and consisted of age and sex (male, female), ethnicity (white, non-white), Townsend index of material deprivation[450], and education (university degree, no degree), tobacco use (current or never/former), and body mass index (BMI, kg/m^2). Continuous variables were centred to a mean of zero.

Field IDs of UK Biobank variables used in this analysis are in **Supplementary Table C-1**.

4.2.2.2 Neuroimaging data

The UK Biobank imaging study is a large-scale population-based initiative designed to collect multimodal imaging data to investigate the relationship between brain structure, function, and long-term health outcomes[309]. Data were acquired using Siemens Skyra 3T MRI scanners at four dedicated imaging centres. In this study, I made use of pre-processed resting state functional MRI (rfMRI) and diffusion MRI (dMRI) data generated by an image-processing pipeline developed and run on behalf of UK Biobank[5; 309; 420].

4.2.2.2.1 Resting state fMRI

4.2.2.2.1.1 Data pre-processing

For this study, I used the rfMRI data collected during the first imaging visit which had been pre-processed and registered to standard space ("filtered_func_data_clean_standard.nii.gz")[5]. These images in the UK Biobank pipeline represent pre-processed rfMRI data that have undergone a series of processing steps to prepare them for large-scale analyses by removing noise and registering them to MNI152 standard space. Each participant underwent a 6-minute rfMRI scan, resulting in 490 time points per session. Images from Phase 3 onwards were included in this study. Phase 1 and 2 were the initial imaging protocols, consisting of approximately 500 subjects. For simplicity, this small number of participants were excluded as they

had additional timepoints in the rfMRI scans. Images were acquired with a spatial resolution of 2.4 × 2.4 × 2.4 mm, a TR of 0.735s, and TE of 39ms.

A preprocessing pipeline for rfMRI data in the UK Biobank was implemented to ensure data quality and consistency across a large dataset. The pipeline is described in detail elsewhere, with a brief description provided here (for more detail, see: [5]). Motion correction was applied using MCFLIRT to align volumes and correct for head movement. Grand-mean intensity normalisation was performed to standardise the signal across the 4D dataset using a single multiplicative factor. High-pass temporal filtering was applied with a Gaussian-weighted least-squares straight-line fitting approach, setting the sigma value to 50s to remove low-frequency drifts.

Distortion correction utilised EPI unwarping, using B0 fieldmaps derived from spin-echo acquisitions, alongside gradient distortion correction to correct spatial distortions caused by magnetic field inhomogeneities. Independent Components Analysis (ICA)-based denoising was performed using FMRIB's ICA-based X-noiseifier (FIX). FIX was trained on 40 hand-labelled rfMRI datasets from UK Biobank, achieving high classification accuracy for non-artefactual components and artifact components during validation. The functional data was registered to the T1-weighted structural images using a boundary-based registration (BBR) cost function, with transforms subsequently used to register data to MNI152 standard space. At this stage, no low-pass filtering or additional spatial smoothing was applied. This pre-processed dataset for each participant was then transformed from individual T1 space to MNI152 standard space using the transforms used to register the structural data. The resulting pre-

processed rfMRI images were registered to MNI152 standard space. The directory for the relevant file is:

<subjID>/fMRI/rfMRI.ica/reg_standard/filtered_func_data_clean_standard.nii.gz

Automated quality checks were implemented at each preprocessing step, including measures such as framewise displacement to flag participants with excessive motion. Additionally, visual inspection was conducted on a subset of images to confirm successful preprocessing and alignment, ensuring the reliability of the data for downstream analyses.

4.2.2.2.1.2 Definition of region of interest masks

I created binary masks for seven regions of interest (ROI) which are important to the DPMS: the rostral ventromedial medulla (RVM), periaqueductal grey (PAG), hypothalamus, amygdala, rostral anterior cingulate cortex (rACC), subgenual ACC (sgACC), and dorsolateral prefrontal cortex (dlPFC).

The RVM mask was drawn by hand in FSLeyes using Duvernoy's Atlas of the Human Brainstem and Cerebellum, a reference for brainstem anatomy[331], as a guide. The atlas was used to identify anatomical landmarks on axial slices of the brainstem, and to guide the mask's alignment with the location of the RVM within the medulla and to minimise contamination from adjacent structures. The following landmarks were used: nucleus raphe magnus and adjacent nucleus reticularis gigantocellularis medial to the facial nucleus, with a rostrocaudal extent from caudal pole of facial nucleus to trapezoid body[155; 156].

The PAG mask was drawn in reference to the work of Ezra et al., who defined an MRI mask of this region using a conservative approach in diffusion MRI space[146]. The mask was manually drawn on the B0 image and cross-referenced with Duvernoy's Atlas, to ensure an accurate representation of PAG boundaries.

The hypothalamus mask was drawn using the MRI atlas of the hypothalamus defined by Baroncini et al. as a guide, which used a combination of histological and high-resolution structural MRI data to identify hypothalamic substructures[30]. Key landmarks such as the optic chiasm, mammillary bodies, and third ventricle were used for segmentation, and the mask boundaries were cross-verified with Duvernoy's atlas.

The amygdala mask was derived from the Harvard-Oxford Atlas, thresholded at 50% probability to ensure inclusion of voxels with a high likelihood of belonging to the amygdala. Thresholding was applied to ensure that only voxels with a high likelihood of belonging to the region of interest were included. The Harvard-Oxford Atlas is a probabilistic anatomical brain atlas developed for neuroimaging applications, widely used to define and localise cortical and subcortical regions[124; 164; 180; 287]. The atlas is based on structural MRI data and provides delineations of anatomical brain regions through probabilistic maps, and is integrated into FSLeyes.

The rACC and sgACC masks were drawn using on the Harvard-Oxford Atlas. Voxels within the anterior cingulate cortex were thresholded at 50% probability. Vogt et al.'s histological delineations of cingulate subregions was then used to derive the rACC and sgACC from this region[475]. A grey matter mask was applied to exclude white matter

and cerebrospinal fluid (CSF) using FSL's FAST segmentation tool, ensuring that analyses focused exclusively on grey matter regions relevant to the study.

The dlPFC mask was constructed by combining Harvard-Oxford Atlas regions corresponding to Brodmann areas 8, 9, 46, and 9/46[90]. These regions were thresholded at 50% probability, and a grey matter mask was also applied.

All masks were created on a MNI152 1mm standard space template, and transformed to MNI152 2mm space using FIRST, ensuring compatibility with subsequent analyses **(Table 4-1, Figure 4-2, Figure 4-3).**

ROI Mask	Key Sources	Description
RVM	Duvernoy's Atlas of the Human Brainstem and Cerebellum (Naidich, 2009)[331]	Hand drawn in FSLeyes using Duvernoy's Atlas in reference to nucleus raphe magnus, nucleus gigantocellularis, and facial nucleus.
PAG	Ezra et al. (2015)[146]; Duvernoy's Atlas of the Human Brainstem and Cerebellum (Naidich, 2009)[331]	Derived from work by Ezra et al., who delineated the PAG using diffusion MRI and the B0 image, cross-referenced with Duvernoy's Atlas for accurate boundary definition.
Hypothalamus	Baroncini et al. (2012)[30]; Duvernoy's Atlas of the Human Brainstem and Cerebellum (Naidich, 2009)[331]	Created using Baroncini et al.'s histological and MRI-based approach with landmarks like the optic chiasm and mammillary bodies; boundaries refined using Duvernoy's Atlas.
Amygdala	Harvard-Oxford Atlas (Frazier et al., 2005; Desikan et al., 2006; Makris et al., 2006) [124; 164; 180; 287]	Derived from the Harvard-Oxford Atlas with a 50% probability threshold to include voxels highly likely to belong to the amygdala.
rACC	Vogt et al. (2003)[475]; Harvard-Oxford Atlas	Based on Vogt et al. histological delineation of the ACC and the Harvard-Oxford Atlas, thresholded at 50% probability and refined with grey matter mask.
sgACC	Vogt et al. (2003)[475]; Harvard-Oxford Atlas	Developed using Vogt et al. ACC delineation combined with the Harvard-Oxford Atlas, with a 50% probability threshold applied and refined with grey matter mask.
dlPFC	Harvard-Oxford Atlas; Brodmann Areas (8, 9, 46, 9/46); Cieslik et al. (2012)[90]	Constructed by combining Harvard-Oxford regions corresponding to Brodmann Areas 8, 9, 46, and 9/46, thresholded at 50% probability and refined with a grey matter mask.

Table 4-1. Summary of how binary regions of interest (ROI) masks in the descending pain modulation system (DPMS) were derived.

All ROIs are bilateral and in 2mm MNI152 space. RVM, rostral ventromedial medulla. PAG, periaqueductal grey. rACC, rostral anterior cingulate cortex. sgACC, subgenual anterior cingulate cortex. dlPFC, dorsolateral prefrontal cortex.

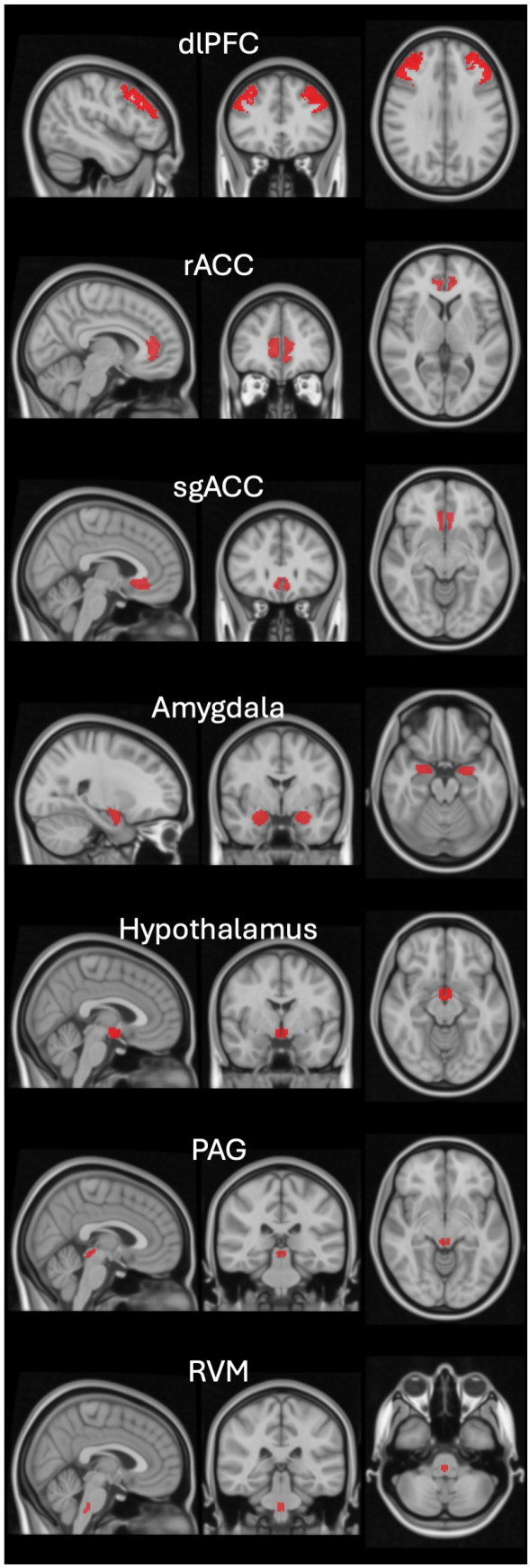


Figure 4-2. Two-dimensional (2D) representation of the region of interest masks of DPMS

All masks are in red, overlayed on MNI152 standard space brain. DPMS, descending pain modulation system. RVM, rostral ventromedial medulla. PAG, periaqueductal grey. rACC, rostral anterior cingulate cortex. sgACC, subgenual anterior cingulate cortex. dlPFC, dorsolateral prefrontal cortex.

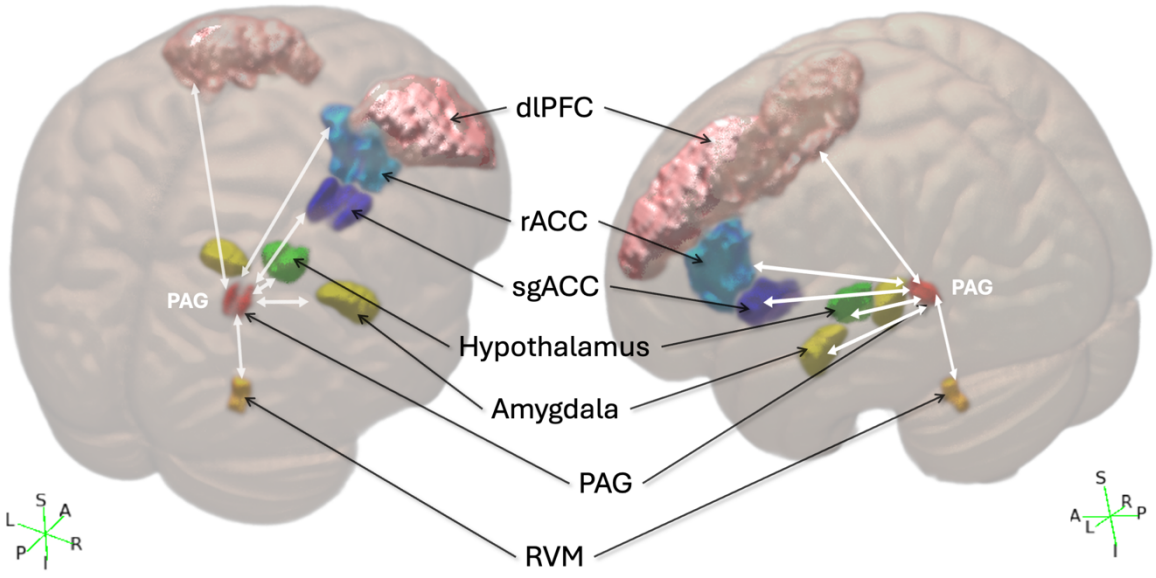


Figure 4-3. Three-dimensional (3D) representation of the region of interest masks of DPMS evaluated in this study.

Masks are overlayed on 3D MNI152 standard space brain. DPMS, descending pain modulation system. RVM, rostral ventromedial medulla. PAG, periaqueductal grey. rACC, rostral anterior cingulate cortex. sgACC, subgenual anterior cingulate cortex. dlPFC, dorsolateral prefrontal cortex. S, superior. I, inferior. A, anterior. P, posterior. L, left. R, right.

4.2.2.2.1.3 Estimation of functional connectivity matrices

The mean 4-D time-series data within each ROI were extracted for each participant using `fslmeants` from FSL. Participants with fewer or greater than 490 time points (indicative of incomplete resting-state scans) or incomplete data extraction for all ROIs were excluded. Time-series data were pre-processed using a custom R function based on `nets_load` from FSLnets. Preprocessing steps included demeaning and variance-normalising the time series for each participant, followed by concatenation into a single matrix for group-level analyses. As a quality check, spectral analysis was performed using a custom R pipeline based on `nets_spectra` from FSLnets to ensure the quality and stability of the time-series data. For each ROI, the mean power spectrum was computed, averaged across participants, and plotted for visually inspection.
Functional connectivity network matrices ("netmats") were computed for each participant using custom R scripts based on `netmats` from FSLnets. Partial correlations were calculated to estimate functional connectivity between ROIs, generating 21 unique connectivity pairs, representing one half of the correlation matrix from seven ROIs. These were derived by inverting the covariance matrix of the time-series data and normalising using the diagonal elements of the inverted matrix. Diagonal elements were set to zero to remove self-connections, and Fisher's R-to-z transformation was applied to normalise correlation coefficients across participants. Diagnostic checks included validation of matrix inversion and identification of out-of-range values. The resulting connectivity matrices were compiled into a data frame for further analyses.
Values were standardised to a mean of 0, and SD of 1. To reduce the influence of outliers, functional connectivity values were winsorised at ±3SD from the mean.

Winsorising avoids removing extreme values, instead trimming them to an upper and lower limit[185].

For the analysis, six connectivity pairs from the PAG were evaluated: RVM-PAG, PAG-Hypothalamus, PAG-Amygdala, PAG-rACC, PAG-sgACC, and PAG-dlPFC (**Figure 4-3**).

4.2.2.2.2 Diffusion-weighted MRI

In addition to functional connectivity, I also estimated structural connectivity between four key nodes of the DPMS: RVM, PAG, amygdala, and hypothalamus, using probabilistic tractography. Probabilistic tractography is an analysis method used to map structural connections in the brain based on diffusion-weighted MRI (dMRI) data[34]. It estimates the most likely pathways of white matter tracts by modelling the uncertainty in fibre orientation at each voxel. Unlike deterministic tractography, which uses a single principal direction, probabilistic approaches consider distributions of possible fibre directions, allowing for the reconstruction of more complex pathways, including crossing or diverging fibres. This method is useful for studying the connectivity of specific brain regions or networks, as it provides a probabilistic map of connectivity distributions rather than a binary connection pathway.

4.2.2.2.2.1 Data pre-processing

The preprocessing of diffusion-weighted imaging (DWI) data from UK Biobank was carried out previously, and is described in detail elsewhere[6]. Briefly, preprocessing involved addressing scanner-induced distortions and preparing data for tractography. The generation of the merged and binary brain mask input files involved preprocessing

steps applied to the raw diffusion-weighted MRI (dMRI) data. Gradient distortion correction was performed to address spatial distortions arising from the scanner's magnetic field non-linearities. The data were then processed using FSL's Eddy tool to compensate for distortions caused by eddy currents and participant motion during image acquisition. After these corrections, the diffusion-weighted volumes, including the non-diffusion-weighted (b=0) images, were normalised and concatenated into a single 4D image file, referred to as the merged file. The b=0 images were extracted, averaged to enhance the signal-to-noise ratio, and processed using FSL's Brain Extraction Tool (BET) to generate a binary brain mask ("nodif_brain_mask") that delineated brain from non-brain tissues. This mask provided a spatial constraint for subsequent tractography.

To ensure alignment across participants, spatial transformations between dMRI space and MNI152 standard space were computed using FSL tools `convertwarp` and `invwarp`. Input files included a fieldmap image, a warp image, and a diffusion-weighted image ("dti_S0"). Forward ("diff2seed") and inverse ("seed2diff") transformation matrices were generated with a reference image in standard space ("MNI152_T1_1mm"). These transformation matrices were used to map tractography results between diffusion and standard space, ensuring alignment across participants.

4.2.2.2.3 Probabilistic tractography

Probabilistic tractography was performed using FSL's probtrackx2 to estimate structural connectivity distributions between seven ROIs from four key DPMS nodes, the RVM, PAG, left and right amygdala and left and right hypothalamus[34]. The higher

cortical regions (ACC and dlPFC) were excluded due to computational constraints. Binary seed masks for these ROIs were defined in diffusion space, using the same masks outlined earlier, and a midline exclusion mask was applied to avoid implausible pathways crossing the corpus callosum. Tractography parameters included 5,000 probabilistic samples per voxel, and the default settings of a step length of 0.5 mm, a curvature threshold of 0.2 radians, and fibre volume and distance thresholds of 0.01 and 0.0, respectively. Input files included the merged diffusion-weighted image and the associated binary brain mask ("nodif_brain_mask"). Results were stored as voxel-wise connectivity maps in participant-specific directories.

Participant-specific connectivity matrices ("fdt_network_matrix.txt") were processed to calculate average connectivity values for the predefined region pairs. Symmetric pairs (e.g., RVM-PAG and PAG-RVM) were averaged to account for directional redundancy. Self-pairings (e.g., RVM-RVM) were excluded from analysis. This resulted in 21 unique structural connectivity pairs. The processed region-pair connectivity data were saved as participant-specific CSV files with column headers corresponding to region pairs. Connectivity data from all participants were consolidated into a single dataset by appending participant identifiers (extracted from filenames) as a new column. Quality checks were performed to ensure no duplicate or missing identifiers, and the final dataset was saved for further analyses. For analyses, the mean of left and right edges for structural connectivity was used to reduce the number of comparisons, as preliminary analyses indicated similar associations for each side. Values were mean-centred, standardised, and winsorised as described above. This left six unique

structural connectivity pairs for analysis: RVM-PAG, RVM-Hypothalamus, RVM-Amygdala, PAG-Hypothalamus, PAG-Amygdala, and Hypothalamus-Amygdala.

4.2.3 Objectives 1&2: Relationship between DPMS Connectivity and nociplastic pain severity

The FMI was used as a continuous measure of nociplastic pain severity, as outlined in chapter 3 (Section 3.2.3.1). To evaluate the relationship between connectivity pairs (edges) in the DPMS and nociplastic pain severity, I used generalised additive models (GAM) using the `gam()` function from the `mgcv` package in R. GAMs are suited for this analysis as they allow for flexible modelling of non-linear relationships by combining linear predictors and smooth functions, with smoothness parameters selected using restricted maximum likelihood (REML) estimation. While the beta coefficients of individual terms in a GAM are less interpretable than a linear model, my primary interest was in assessing the overall significance of connectivity pairs in the model.

For both functional and structural connectivity, two GAM models were fitted to evaluate the associations: a minimally-adjusted model including imaging confounders, and a fully-adjusted model additionally adjusted for socioeconomic and lifestyle confounders.

4.2.3.1.1 Imaging confounds

Imaging confounders comprised age, sex, imaging centre, scan date, head size, table position (head centre of gravity on the X, Y, and Z axes), and mean head motion during resting-state fMRI (no estimate of head motion from the diffusion scan was available).

As scan day and time between imaging and pain assessment were collinear, only scan day was included as a covariable. These imaging confounders were selected based on prior literature on confound modelling in UK Biobank neuroimaging data[7].

4.2.3.1.2 Socio-demographic & lifestyle confounds

The fully-adjusted model added socio-demographic and lifestyle variables, consisting of education level (degree vs. no degree), Townsend index of deprivation, self-reported ethnicity (white vs. non-white), smoking status (current vs. non-smoker), and BMI. Continuous variables were modelled as smooth terms to account for potential non-linear effects.

4.2.3.1.3 Generalised additive models

Smooth terms were modelled using thin-plate regression splines, with smoothness parameters estimated via REML. The number of knots (k) was not manually specified and was determined automatically by `mgcv` using generalised cross validation (GCV), which balances model complexity and overfitting[504]. Model fit was evaluated using R^2 and GCV score.

To quantify the contribution of connectivity, the incremental R^2 was calculated as the difference in R^2 values between the minimally-adjusted and fully-adjusted models. Overall significance was evaluated using ANOVA to compare the fit of the reduced and full models.

Bonferroni correction was applied to adjust p-values for multiple testing across the number of connectivity pairs in the model, to reduce the risk of Type I error. A corrected alpha of 0.05 was deemed significant for all analyses. Smooth plots for each connectivity pair were annotated with effect sizes, degrees of freedom, and Bonferroni-

adjusted p-values. Diagnostic plots, including residual checks and smooth term visualisations, were generated to evaluate model assumptions.

4.2.3.2 Objectives 1&2: Stratification by chronic pain status

To evaluate whether the relationship between DPMS connectivity and nociplastic pain severity differed based on chronic pain status at the time of questionnaire, interaction analyses were conducted for both RSFC and structural connectivity. Chronic pain status was derived from the 2019 pain questionnaire (See chapter 3, Section 3.2.3.1) and modelled as a binary variable, indicating the presence or absence of pain for 3+ months. Interaction terms were included between chronic pain status and each DPMS connectivity pair in the models.

4.2.3.2.1 Statistical analysis

As the main effects of interest were linear, linear models were used to assess these interactions. Each analysis included two models for comparison: a reduced model that incorporated the main effects of connectivity pairs, chronic pain status, and covariates, and a full model that included interaction terms between chronic pain status and connectivity pairs. The same covariates as described in sections 4.2.3.1.1 and 4.2.3.1.2 were used.

The overall significance of the interaction terms was tested using likelihood ratio tests (LRT) comparing the full and reduced models. R^2 values were computed for both models, and the percentage increase in explained variance (ΔR^2) due to the interaction terms was calculated. As above, Bonferroni correction was applied to adjust p-values

for multiple testing across connectivity pairs. The same approach was applied for the structural connectivity analysis.

4.2.4 Objective 3: Mediation with executive function

To evaluate whether changes in functional or structural connectivity in the DPMS mediate the association between nociplastic pain severity and executive function, mediation analyses were conducted using structural equation modelling (SEM). A latent factor for executive function was constructed as described in Chapter 3 (Section 3.2.4.1). Separate SEM models were specified for functional and structural connectivity measures. Each model included FMI as the explanatory variable, connectivity measures as mediators, and executive function as the outcome. Both models adjusted for the same covariates outlined in Sections 4.2.3.1.1 and 4.2.3.1.2.

Indirect effects for each connectivity pair were calculated as the product of the path coefficients linking DPMS connectivity to FMI and FMI to executive function. Total effects were computed as the sum of direct and indirect effects. The models were estimated using maximum likelihood. Bias-corrected bootstrapping with 5,000 resamples was used to test the significance of the direct, indirect, and total effects, which accommodates non-normal distributions of indirect effects[85]. The significance of mediation effects was assessed using standardised parameter estimates, with Bonferroni correction applied to the indirect paths. Model fit was evaluated using Comparative Fit Index (CFI), Tucker Lewis Index (TL), and Root Mean Square Error of Approximation (RMSEA).

4.2.5 Objective 4: Interaction between DPMS connectivity and biopsychosocial characteristics

To explore the multivariate relationships between RSFC within the DPMS and biopsychosocial characteristics relevant to chronic pain, I conducted canonical correlation analysis (CCA). This approach allows the identification of modes of covariation between these imaging and behavioural datasets, providing insight into how DPMS connectivity patterns are associated with behavioural and health-related traits at a population level.

4.2.5.1 Data Preparation

Outcomes and explanatory variables were extracted from the UK Biobank dataset for participants with available imaging and non-imaging data. The outcome variables (non-imaging phenotypes) represented a set of biopsychosocial measures associated with nociplastic pain: fatigue (FSS), depressive symptoms (PHQ-9), neuroticism[419], subjective cognitive difficulties, sleep quality (self-reported sleep duration, insomnia symptoms, and unrefreshing sleep), widespread pain, and self-rated health (**Table 4-2**). These measures were selected based on their relevance to nociplastic pain and were pre-processed as described in chapter 3 (Section 3.2.3.3).

RSFC metrics, the explanatory variables, were derived from pairwise connectivity between the seven predefined DPMS nodes described in section 4.2.2.2.1.2 (**Figure 4-3**). RSFC was computed as Fisher-z-transformed partial correlation coefficients between node-pair timeseries for seven ROIs, yielding a 21-feature set representing functional connections across the DPMS network.

Work by other groups on UK Biobank has included a dimensionality-reduction step with principal components analysis (PCA) prior to performing CCA[279; 422]. However, given the relatively constrained selection of variables selected (brain regions relevant to the DPMS and behavioural measures relevant to pain), this was not performed. To ensure comparability, all variables were standardised (z-scored) by centring and scaling before further analysis.

Biopsychosocial variable	Description
Widespread Pain Index	From Fibromyalgia Index (Pain Questionnaire)
Brain-fog severity	From Fibromyalgia Index (Pain Questionnaire)
Fatigue severity	From Fibromyalgia Index (Pain Questionnaire)
Unrefreshing sleep severity	From Fibromyalgia Index (Pain Questionnaire)
Fatigue severity score (FSS)	Pain Questionnaire
Depression (PHQ-9)	Pain Questionnaire
Self-rated health (EQ-5D-5L VAS)	Pain Questionnaire
Number of chronic pain sites (0-7)	Collected during imaging visit
Neuroticism score	Collected during imaging visit
Self-reported sleep duration	Collected during imaging visit
Insomnia symptoms	Collected during imaging visit

Table 4-2. Summary of biopsychosocial and pain characteristics included in canonical correlation analysis (CCA).

Nociplastic pain assessed using the fibromyalgia index (FMI), with higher scores indicating more severe nociplastic pain. The FMI is the sum of the widespread pain index (WPI) and symptom severity scale (SSS). Brain-fog, fatigue, and unrefreshing sleep measured using items from the SSS, with higher scores indicating more severe symptoms. Fatigue measured using the Fatigue Severity Scale (FSS) on the pain questionnaire, with higher scores indicating more severe fatigue symptoms. Note this questionnaire was only offered to participants who reported fatigue on the SSS. Depression measured using Patient Health Questionnaire 9-item on the pain questionnaire, with higher scores indicating more severe depression symptoms. Self-rated health using visual analogue scale from EuroQoL 5D 5L questionnaire, with higher scores indicating better health status. Neuroticism score derived from a count of symptoms in touchscreen assessment at imaging visit, described by Smith et al. (2013), SD, standard deviation. The Pain Questionnaire was conducted online in 2019.

4.2.5.1.1 Adjustment for confounders

To account for potential confounding variables, separate regression models were applied to the explanatory and outcome variable sets. RSFC metrics were regressed against the imaging and socio-demographic confounds described in sections 4.2.3.1.1 and 4.2.3.1.2. Behavioural outcome variables were adjusted the socio-demographic variables described in section 4.2.3.1.2. Residuals from these models were extracted and visually inspected using boxplots to confirm the removal of systematic bias. These residuals were used as the inputs for subsequent CCA.

4.2.5.2 Statistical analysis

CCA was performed to investigate multivariate relationships between RSFC metrics (explanatory variables) and behavioural outcomes (outcome variables). This technique identifies pairs of canonical variates—linear combinations of variables from the two datasets, called 'modes'—that maximise their mutual correlation[12; 206; 279]. Each mode represents an axis of covariation between RSFC metrics and behavioural traits. The analysis was conducted using the `CCA` package in R. To ensure robust inferences, statistical significance was determined via permutation testing (5,000 permutations), where the rows of the outcome variables were shuffled to generate a null distribution of canonical correlations.

Loadings (correlations of individual variables with canonical variates) were extracted for both RSFC and behavioural variables, and variables with absolute loadings ≥0.2 were plotted for interpretation[422].

4.2.5.3 Cross-validation and permutation testing

To assess the robustness and generalisability of the canonical correlations, I implemented 10-fold cross-validation[242; 503]. The dataset was randomly partitioned into 10 folds, and for each fold, the analysis was performed on a training set (90%) while testing was conducted on the remaining 10%. Canonical coefficients derived from the training set were applied to the test set, and the correlation between the first canonical variates of the explanatory and outcome variables in the test set was recorded. This process was repeated across folds, and the mean canonical correlation was calculated.

To evaluate the statistical significance of the canonical correlations, permutation testing was integrated into the cross-validation framework. For each training set, outcome variables were permuted 5,000 times, and the resulting null distribution was used to compute p-values for the test set. The mean p-value across folds provided a summary measure of significance, with an alpha set at $P<0.05$.

Cross-validation ensures that the canonical correlation model generalises to unseen data, reducing the likelihood of overfitting[47; 337]. Permutation testing further strengthens the analysis by providing an estimate of the likelihood that observed correlations could arise under the null hypothesis of no association. Together, these approaches enhance confidence in the robustness and validity of the reported canonical correlations.

All cross-validation and permutation testing procedures were implemented using custom functions developed with the `caret` package in R.

4.3 Results

4.3.1 Study participants

Of the 167,185 UK Biobank participants who completed the 2019 pain questionnaire, functional connectivity (rs-fMRI) data were available for 42,895 (71.1%) participants scanned between May 2014 and June 2023, while structural connectivity (dMRI) data were extracted for a subset of 33,027 participants scanned between August 2014 and April 2022. Functional and structural connectivity metrics were successfully extracted for 99.9% and 98.6% of participants with available fMRI and dMRI imaging data, respectively. The smaller dMRI cohort reflects an earlier data extraction, with less pre-processed data available at the time. Most exclusions were due to unavailable rfMRI or dMRI data, largely because of differences in data availability at the time of analysis. Given that a large proportion of participants did not have a brain MRI (over half of those who completed the 2019 pain questionnaire), and it could not be assumed the data was missing at random, imputation was not performed. A small proportion of participants (<5%) were subsequently excluded due to missing pain questionnaire responses or incomplete confounder data (e.g., head size, scan date, head motion), leaving a sample size of 44,411 for the functional connectivity, and 33,027 for the structural connectivity, analyses. Given this small proportion, a complete case analysis was appropriate[432]. The flow diagram summarises the inclusion and exclusion for both analyses (**Figure 4-4**).

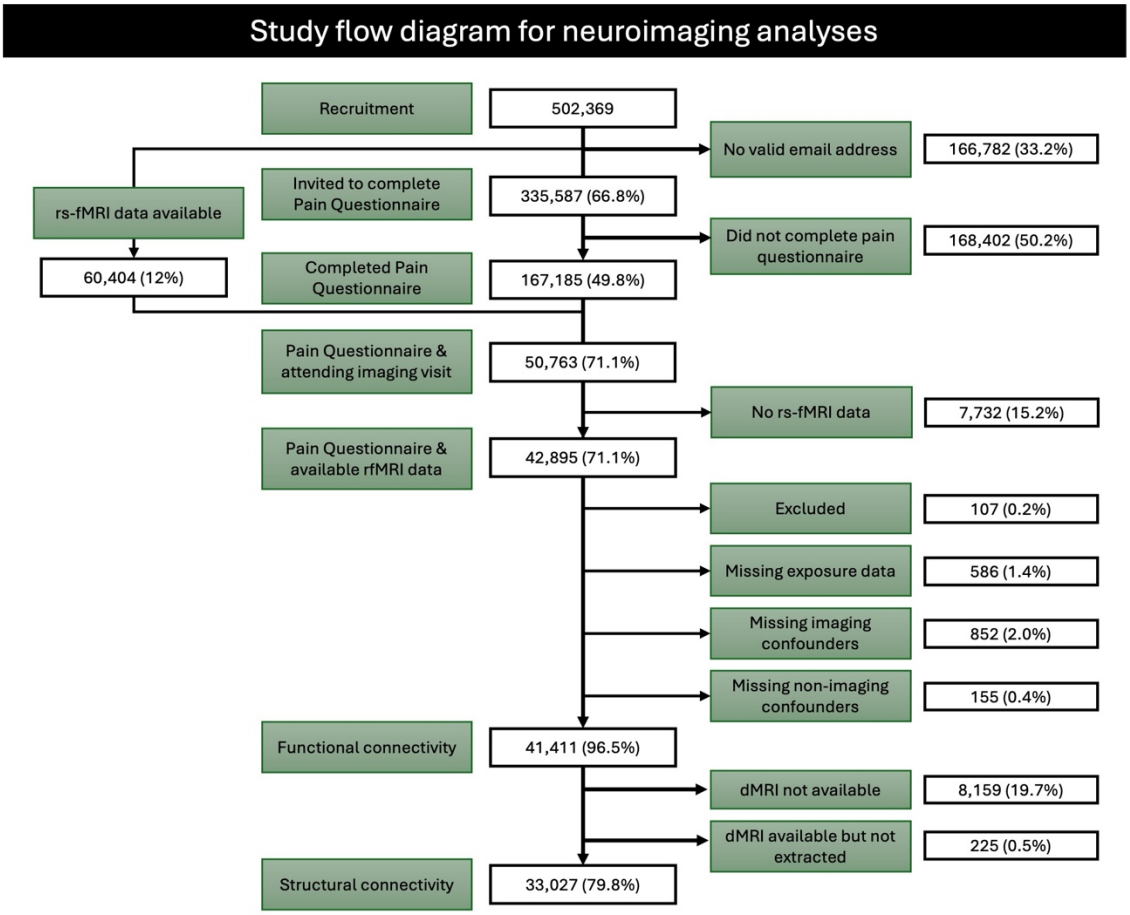


Figure 4-4. Study flow diagram for UK Biobank participants included in analyses of DPMS connectivity and nociplastic pain severity.

Functional connectivity (rs-fMRI) data were available for 41,411 participants scanned between May 2014 and June 2023, while structural connectivity (dMRI) data were extracted for a subset of 33,027 participants scanned between August 2014 and April 2022. The smaller dMRI cohort reflects an earlier data extraction to reduce computational intensity, focusing only on participants who completed the 2019 Pain Questionnaire. The "Excluded" group comprises participants with major neurological condition at baseline who were excluded from this analysis. DPMS, descending pain modulation system. dMRI, diffusion-weighted MRI. Rs-fMRI, resting state functional MRI.

4.3.2 Baseline characteristics

Baseline characteristics of participants included in the functional connectivity analysis are detailed in **Table 4-3**. The mean age was 64.7 years (SD 7.61), 54% were female. Most participants were retired (59%) and predominantly of white ethnicity (97.4%). Most (71%) reported weekly or daily alcohol consumption, while only 3.1% were current smokers. The mean BMI was 26.3 kg/m^2.

Participants with chronic pain (53% of the cohort) showed higher nociplastic pain severity compared to those without chronic pain, with mean WPI scores of 2.18 vs 0.28 and mean SSS scores of 2.94 vs 1.69. Sociodemographic and lifestyle factors were largely similar between groups, although a slightly higher proportion of chronic pain participants were female (58% vs 50%). There were some minor differences between the functional and structural connectivity subgroups, but overall the groups were similar (Supplementary Table C-2 & Supplementary Table C-3).

	Total	No Chronic pain	Chronic pain
	(N=41411)	(N=19272)	(N=22139)
Female, N (%)	22375 (54 %)	9616 (50 %)	12759 (58 %)
Age, mean (SD) years	64.7 (7.61)	64.6 (7.63)	64.8 (7.59)
Townsend Deprivation Index, mean (SD)	-1.90 (2.73)	-1.96 (2.70)	-1.86 (2.75)
Married/Partner N (%)	30866 (75 %)	14458 (75 %)	16408 (74 %)
Employment status			
Employed	15087 (36 %)	7290 (38 %)	7797 (35 %)
Retired	24580 (59 %)	11288 (59 %)	13292 (60 %)
Unemployed/Other	1509 (4 %)	590 (3 %)	919 (4 %)
White Ethnicity, N (%)	42516 (97.4%)	18790 (97.5%)	21541 (97.3%)
University Degree, N (%)	21327 (51.5%)	10445 (54.2%)	10892 (50%)
Current tobacco use, N (%)	1265 (3.1%)	561 (1.7%)	704 (3.2%)
Alcohol Use			
Never	2695 (7 %)	1171 (6 %)	1524 (7 %)
Rarely	9010 (22 %)	3886 (20 %)	5124 (23 %)
Weekly	22493 (54 %)	10773 (56 %)	11720 (53 %)
Daily	6971 (17 %)	3334 (17 %)	3637 (16 %)
Body Mass Index, mean (SD) kg/m2	26.3 (4.38)	25.9 (4.08)	26.8 (4.58)
Fibromyalgia Index (0-31), mean (SD)	3.66 (3.55)	1.97 (1.93)	5.13 (3.96)
Widespread Pain Index (0-19), mean (SD)	1.30 (2.00)	0.279 (0.752)	2.18 (2.30)
Symptom Severity Scale (0-12), mean (SD)	2.36 (2.11)	1.69 (1.64)	2.94 (2.30)

Table 4-3. Baseline characteristics of participants included in analysis of DPMS connectivity and nociplastic pain severity.

Sociodemographic, lifestyle, pain-related, and cognitive performance metrics are summarised for participants in the functional connectivity (N=41,557) group. Results are presented as percentages, means with standard deviations (SD), or medians with ranges, as appropriate. Higher values of Townsend Deprivation Index indicate greater social deprivation. Nociplastic pain assessed using the fibromyalgia index (FMI), with higher scores indicating more severe nociplastic pain. The FMI is the sum of the widespread pain index (WPI) and symptom severity scale (SSS). SD, standard deviation

4.3.3 Objectives 1&2: Functional connectivity in the DPMS is associated with nociplastic pain severity

RSFC connectivity explained a significant, albeit modest, proportion of variance in FMI (minimally-adjusted LRT P=0.00002; fully-adjusted LRT P=0.0007; ΔR^2=0.000586) (**Figure 4-5**). Despite statistical significance, RSFC explained only 0.063% of FMI variance after adjusting for confounders.

Notably, PAG-amygdala connectivity demonstrated a small nonlinear association with FMI in the minimally adjusted model (F=3.65, P=0.00375; corrected P=0.022), though this was further attenuated after full adjustment (F=3.02, P=0.0175; corrected P=0.105). Other RSFC pairs showed small effect sizes which were not significant after correction for multiple comparisons. See Supplementary Table C-4 for full results.

These findings highlight PAG-amygdala connectivity as a potential marker of nociplastic pain severity, meriting further exploration as a biomarker. However, the small effect sizes observed and minimal variance explained underscores the multifactorial nature of nociplastic pain, suggesting other factors likely play a dominant role.

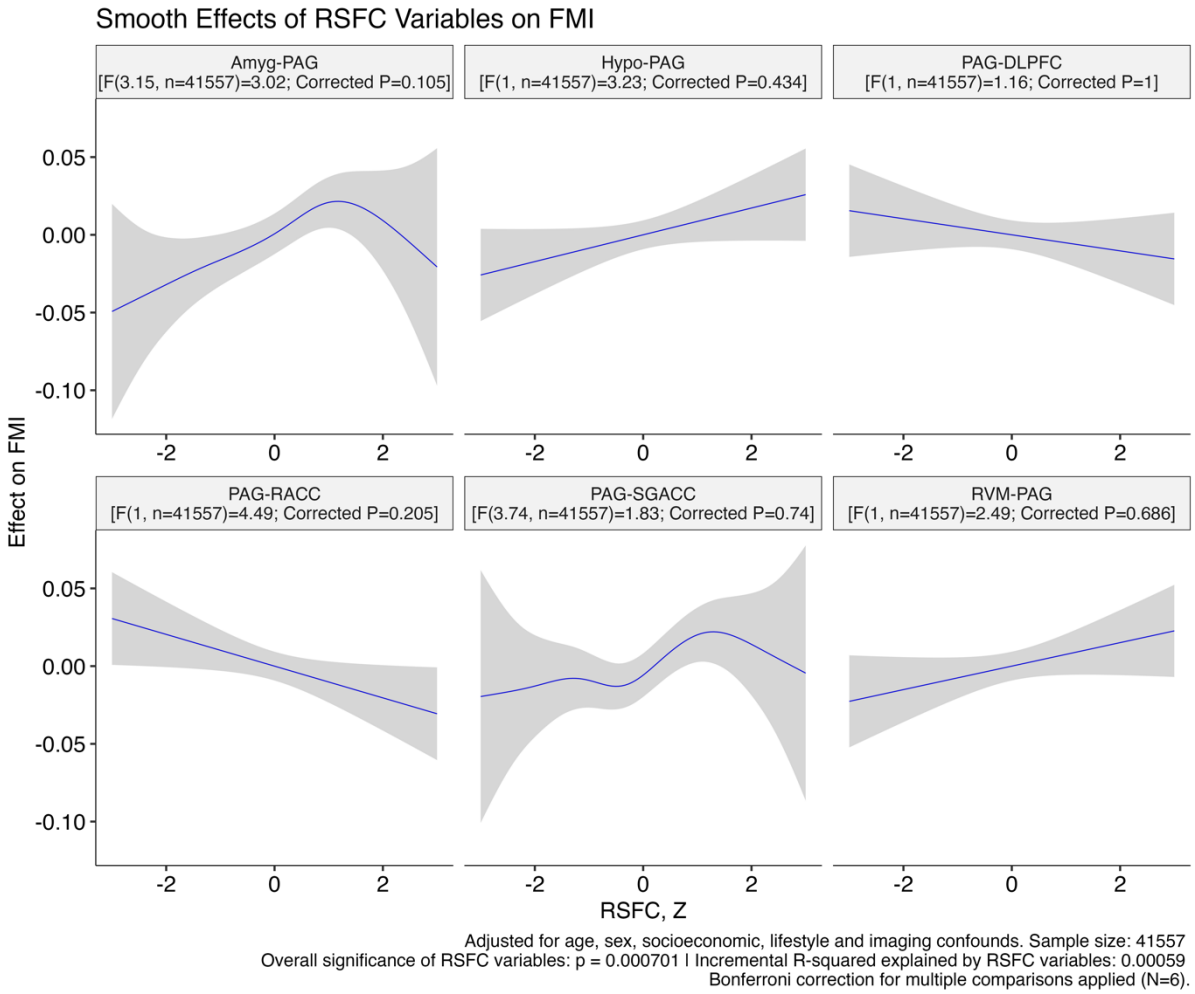


Figure 4-5. Functional connectivity in the DPMS is associated with nociplastic pain severity

Smooth effects of resting-state functional connectivity (RSFC) variables on nociplastic pain severity (fibromyalgia index, FMI) in fully adjusted model. Each panel represents a separate RSFC variable. All scales are standardised to mean=0, SD=1. The blue line indicates the smoothed relationship between RSFC and FMI, with the shaded area representing the 95% confidence interval. Adjusted for age, sex, imaging confounds (head size, table position, scan date, scan site, and head motion), socio-demographics (ethnicity, Townsend index of multiple deprivation, education), and lifestyle (tobacco use, body mass index). PAG, periaqueductal grey. RVM, rostral ventromedial medulla. Amyg, amygdala. Hypo, hypothalamus. rACC, rostral anterior cingulate cortex. sgACC, subgenual anterior cingulate cortex. dlPFC, dorsolateral prefrontal cortex.

4.3.3.1 No interaction between chronic pain status and DPMS functional connectivity on nociplastic pain severity

Chronic pain status did not modify the relationship between DPMS functional connectivity and nociplastic pain severity (FMI). Likelihood ratio tests revealed no significant improvement in model fit when interaction terms were included (LRT P=0.252) compared to the main effects model. This remained unchanged in the fully-adjusted model (LRT P=0.271) (**Figure 4-6**).

Among individual interaction terms, only the interaction with PAG-amygdala connectivity displayed a nominal association with chronic pain status (P=0.0266), but this did not survive correction for multiple comparisons (corrected P=0.16). No other connectivity variables demonstrated significant interaction effects. See Supplementary Table C-5 for full results.

These findings suggest that chronic pain status does not substantially influence the relationship between DPMS functional connectivity and nociplastic pain severity, though the nominal association with PAG-Amygdala connectivity merits further investigation.

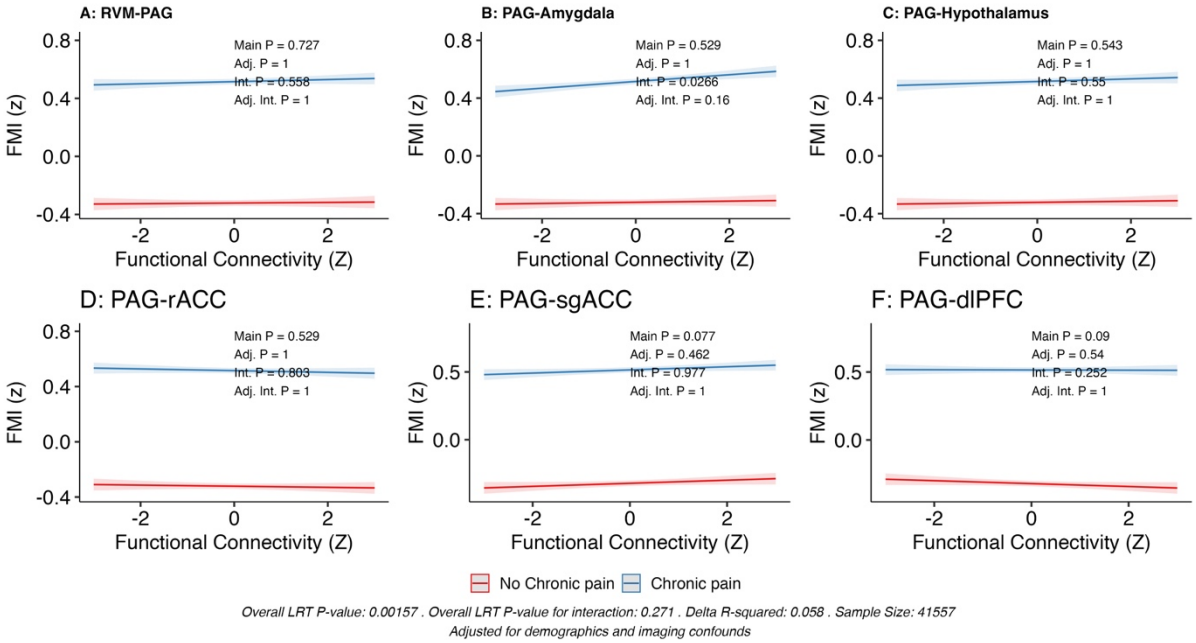


Figure 4-6. No interaction between chronic pain status and DPMS functional connectivity on nociplastic pain severity

Interaction effects of resting-state functional connectivity (RSFC) variables with chronic pain status on nociplastic pain severity (Fibromyalgia Index, FMI) in the fully adjusted model with Bonferroni-corrected P-values. Each panel represents a separate RSFC variable, with the blue (chronic pain, N=22,139) and red (no chronic pain, N=19,272) lines showing the predicted relationship between RSFC and FMI. All scales are standardised to mean=0, SD=1. Shaded areas indicate the 95% confidence intervals. Adjusted for age, sex, imaging confounds (head size, table position, scan date, scan site, and head motion), socio-demographics (ethnicity, Townsend index of multiple deprivation, education), and lifestyle factors (tobacco use, body mass index). PAG, periaqueductal grey. RVM, rostral ventromedial medulla. Amyg, amygdala. Hypo, hypothalamus. rACC, rostral anterior cingulate cortex. sgACC, subgenual anterior cingulate cortex. dlPFC, dorsolateral prefrontal cortex.

4.3.4 Objectives 1&2: Structural connectivity in DPMS is associated with nociplastic pain severity

Structural connectivity within the DPMS was significantly associated with nociplastic pain severity (FMI), although its overall contribution to variance explained was small (LRT P=0.000119; ΔR^2=0.00079). In the fully adjusted model, PAG-amygdala connectivity displayed the strongest association, showing a positive linear relationship with FMI (F(1)=11.55, corrected P=0.004) (**Figure 4-7**). Structural connectivity between the hypothalamus and amygdala demonstrated a small nonlinear association with nociplastic pain severity (F(1.67)=4.86, corrected P=0.039). Other connections, such as RVM-hypothalamus and RVM-amygdala, displayed small nominal associations with FMI but did not survive correction for multiple comparisons (corrected P=0.06 and P=0.086, respectively). See Supplementary Table C-6 for full results. These findings suggest that specific structural pathways within the DPMS, particularly the PAG-amygdala and hypothalamus-amygdala circuits, may play a role in modulating nociplastic pain severity. However, the small effect sizes highlight the need for further exploration of additional mechanisms contributing to nociplastic pain.

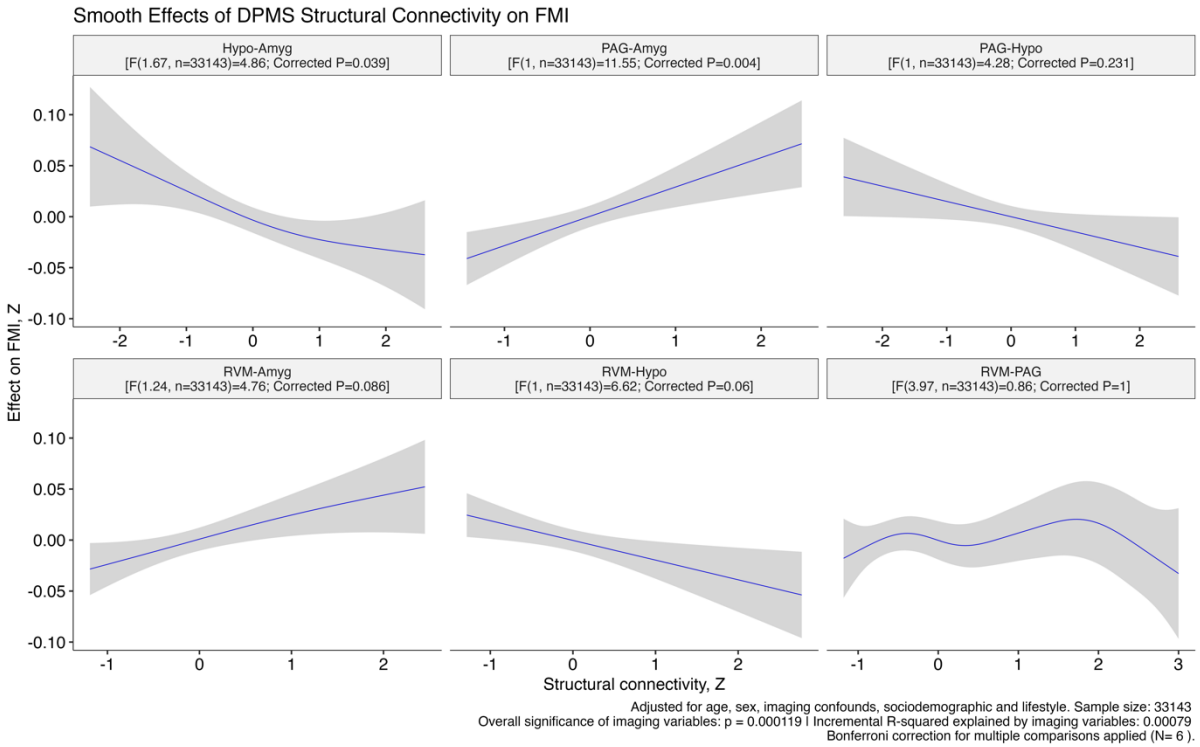


Figure 4-7. Structural connectivity in DPMS is associated with nociplastic pain severity

Smooth effects of structural connectivity variables in the descending pain modulatory system (DPMS) on nociplastic pain severity (Fibromyalgia Index, FMI) in the fully adjusted model. Each panel represents a distinct structural connectivity pair, with the blue line indicating the smoothed relationship between connectivity and FMI, and the shaded region representing the 95% confidence interval. All scales are standardised to mean=0, SD=1. Significant associations are highlighted in the text. Adjusted for age, sex, imaging confounds (head size, table position, scan date, scan site, and head motion), socio-demographics (ethnicity, Townsend deprivation index, education), and lifestyle factors (tobacco use, body mass index). PAG, periaqueductal grey; RVM, rostral ventromedial medulla; Amyg, amygdala; Hypo, hypothalamus.

4.3.4.1 Chronic pain moderates the association between structural connectivity and nociplastic pain severity

The interaction between chronic pain status and structural connectivity within the DPMS significantly influenced nociplastic pain severity (FMI), as shown in **Figure 4-8**. Likelihood ratio testing demonstrated that models including interaction terms explained FMI variance better than main effects-only models (LRT P=0.00109 minimally adjusted; P=0.00174 fully adjusted).

Significant interaction effects were observed for specific structural pathways, including PAG-amygdala connectivity (interaction P=0.00136; corrected P=0.00817). In individuals with chronic pain, higher PAG-amygdala connectivity was associated with increased FMI, a relationship not seen in participants without chronic pain. Similarly, RVM-PAG connectivity demonstrated a significant interaction (interaction P=0.00092; corrected P=0.00551). Chronic pain participants exhibited a positive association between RVM-PAG connectivity and FMI, whereas a negative relationship was observed in those without chronic pain. No significant interactions were observed for other pathways after adjustment for multiple comparisons. See Supplementary Table C-7 for full results.

These results suggest that chronic pain status modulates the relationship between DPMS structural connectivity and nociplastic pain severity, particularly within the PAG-amygdala and RVM-PAG pathways. However, the overall variance explained by these models remains modest, indicating that other factors contribute to nociplastic pain severity.

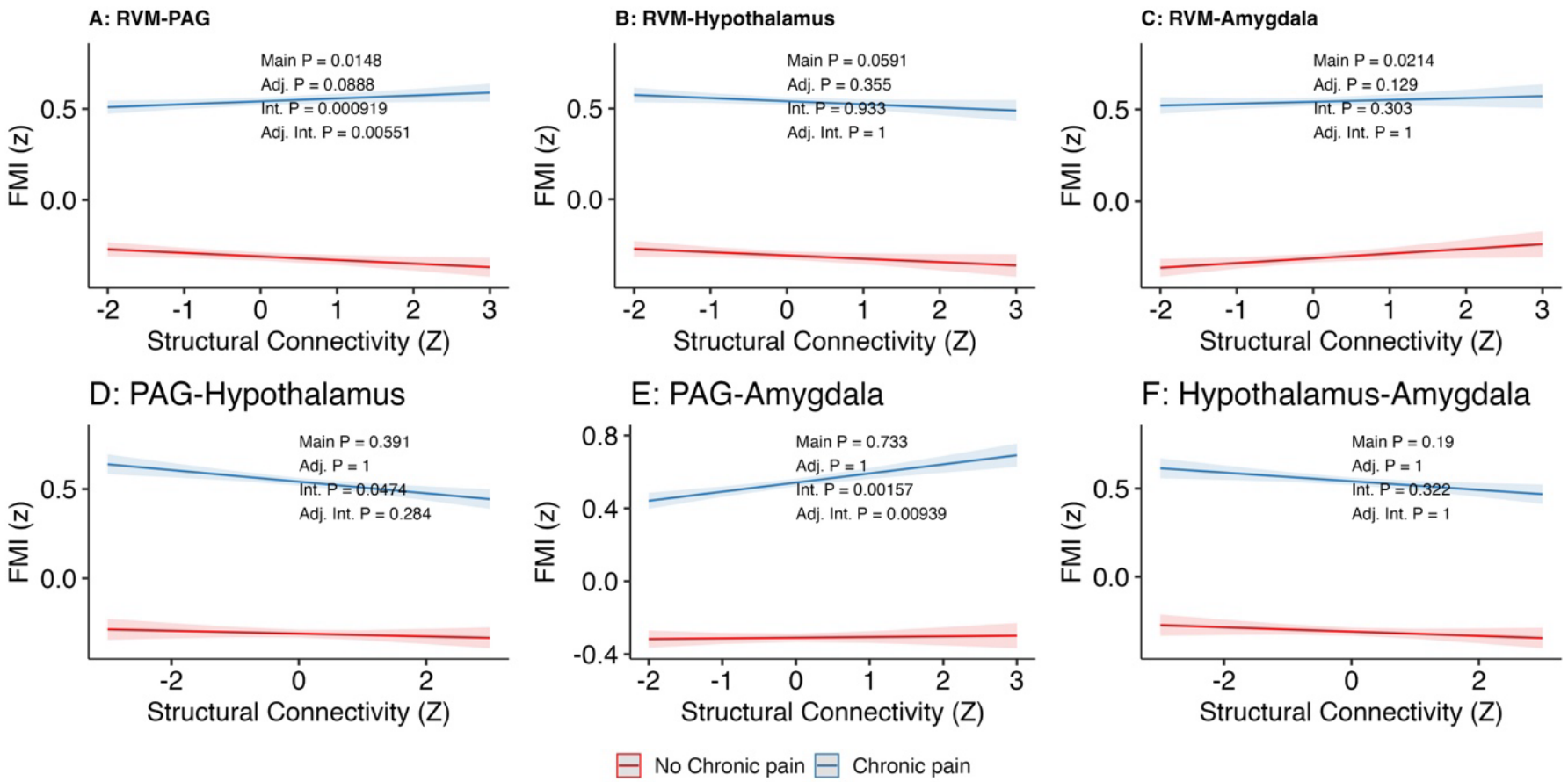


Figure 4-8. Chronic pain moderates the association between structural connectivity and nociplastic pain severity.

Interaction effects of structural connectivity (SC) variables with chronic pain status on nociplastic pain severity (Fibromyalgia Index, FMI) in the fully adjusted model. Each panel represents a separate SC variable, with the blue (chronic pain, N=17,722) and red (no chronic pain, N=15,305) lines showing the predicted relationship between SC and FMI. All scales are standardised to mean=0, SD=1. Shaded areas indicate the 95% confidence intervals. Adjusted for age, sex, imaging confounds (head size, table position, scan date, scan site, and head motion), socio-demographics (ethnicity, Townsend deprivation index, education), and lifestyle factors (tobacco use, body mass index). PAG, periaqueductal grey; RVM, rostral ventromedial medulla; Amyg, amygdala; Hypo, hypothalamus.

4.3.5 Objective 3: Mediation with executive function

The relationship between nociplastic pain severity (FMI) and executive function (EF) was examined using SEM to assess both direct and indirect effects mediated by structural and functional connectivity in the DPMS in participants with chronic pain. This builds on the analyses outlined in chapter 3. Two separate models were constructed: one evaluating functional connectivity and the other focusing on structural connectivity.

4.3.5.1 DPMS functional connectivity does not mediate association with EF

The functional connectivity model demonstrated acceptable fit to the data (Robust CFI=0.897, RMSEA=0.019), indicating good model specification (**Figure 4-9**). Higher FMI scores were significantly associated with reduced EF through a modest direct effect (standardised β=−0.109, 95%CI: −0.141 to −0.077, P<0.001). The total indirect effect via RSFC pathways on the relationship between FMI and EF, however, was small and did not reach statistical significance after Bonferroni correction (β=−0.003, P=0.099). Among specific RSFC pathways, PAG-amygdala connectivity showed a small indirect effect (standardised β=−0.002, corrected P=0.018), indicating that higher FMI was associated with altered PAG-amygdala functional connectivity, which in turn was associated with worse EF, and accounting for 2.1% of the total effect of FMI on EF. Other pathways did not exhibit significant indirect effects after correction. See Supplementary Table C-8 for full results. These results suggest a minimal role of RSFC in mediating the relationship between FMI and EF, with the possible exception of the PAG-amygdala pathway.

4.3.5.2 DPMS structural connectivity mediates association with EF

In contrast to functional connectivity, structural connectivity pathways within the DPMS significantly mediated the relationship between FMI and EF in adults with chronic pain, with notable indirect effects observed for PAG-amygdala and PAG-hypothalamus connectivity (**Figure 4-10**). PAG-amygdala connectivity demonstrated a small negative association with EF (β=−0.0039, corrected P=0.00003), accounting for 3.4% of the total effect, while PAG-Hypothalamus connectivity had a small positive association (β=0.0036, corrected P=0.0079), contributing 3.2% to the total effect.

Although the overall indirect effect across all pathways was small, and non-significant (P=0.493), this likely reflects the opposing directions of individual pathways, with some exerting protective effects (e.g., PAG-hypothalamus) and others deleterious effects (e.g., PAG-amygdala).

Overall, as described in more detail in chapter 3, FMI showed a consistent modest direct negative effect on EF across both RSFC and structural connectivity models. Structural connectivity pathways, especially PAG-amygdala and PAG-hypothalamus, displayed stronger indirect effects compared to functional connectivity. These results suggest that structural alterations within the DPMS in adults with chronic pain may be associated with the executive dysfunction associated with nociplastic pain, warranting further exploration into their mechanistic and therapeutic implications.

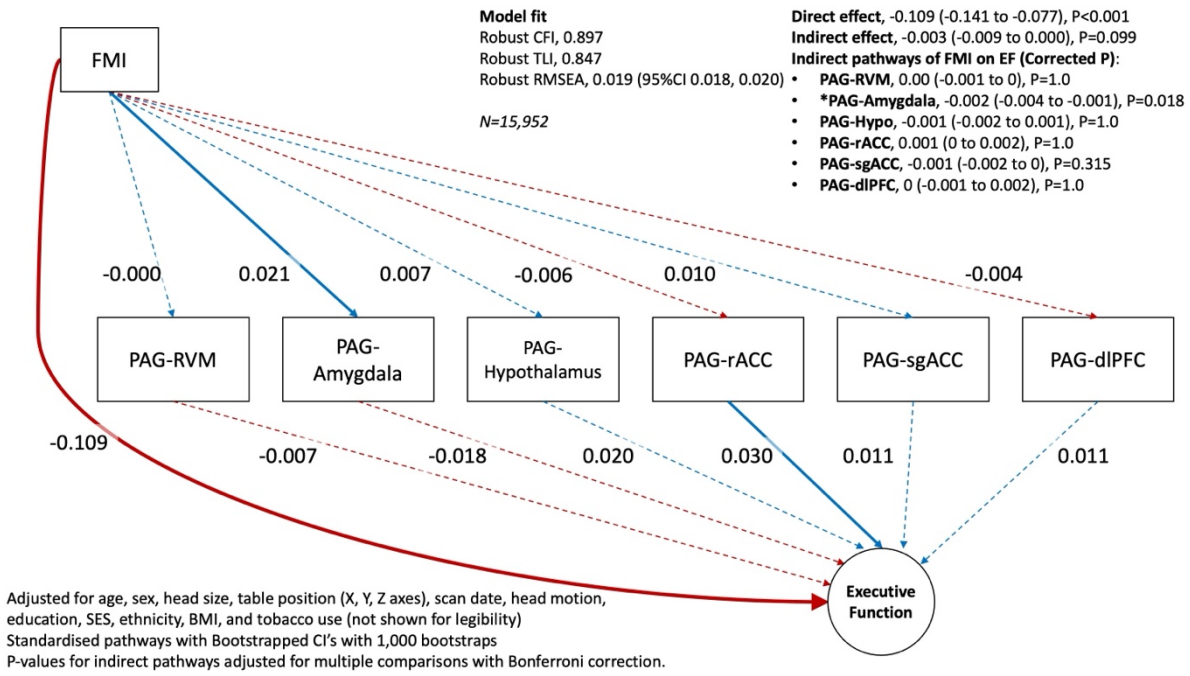


Figure 4-9. PAG-amygdala functional connectivity mediates association with executive function in chronic pain.

Structural equation model of indirect effects of resting-state functional connectivity (RSFC) pathways within the descending pain modulatory system (DPMS) on the association between Fibromyalgia Index (FMI) score and executive function (EF) in adults with chronic pain (N=15,192).
Standardised parameter estimates are presented. Red lines indicate a negative association, while blue lines indicate a positive association. Solid lines represent significant paths, while dashed lines indicate non-significant relationships. Bootstrapped confidence intervals estimated with 5,000 iterations. Higher FMI scores indicate greater nociplastic pain severity, and lower EF scores indicate worse executive function. Only the main pathways are displayed; indicators, exogenous confounders, and covariances between mediators are omitted for clarity. Model fit indices (CFI, TLI, RMSEA) and 95% confidence intervals (CIs) are provided in the figure. P-values for indirect pathways are adjusted for multiple comparisons with Bonferroni correction. PAG, periaqueductal grey; RVM, rostral ventromedial medulla; Amyg, amygdala; Hypo, hypothalamus; rACC, rostral anterior cingulate cortex; sgACC, subgenual anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex.

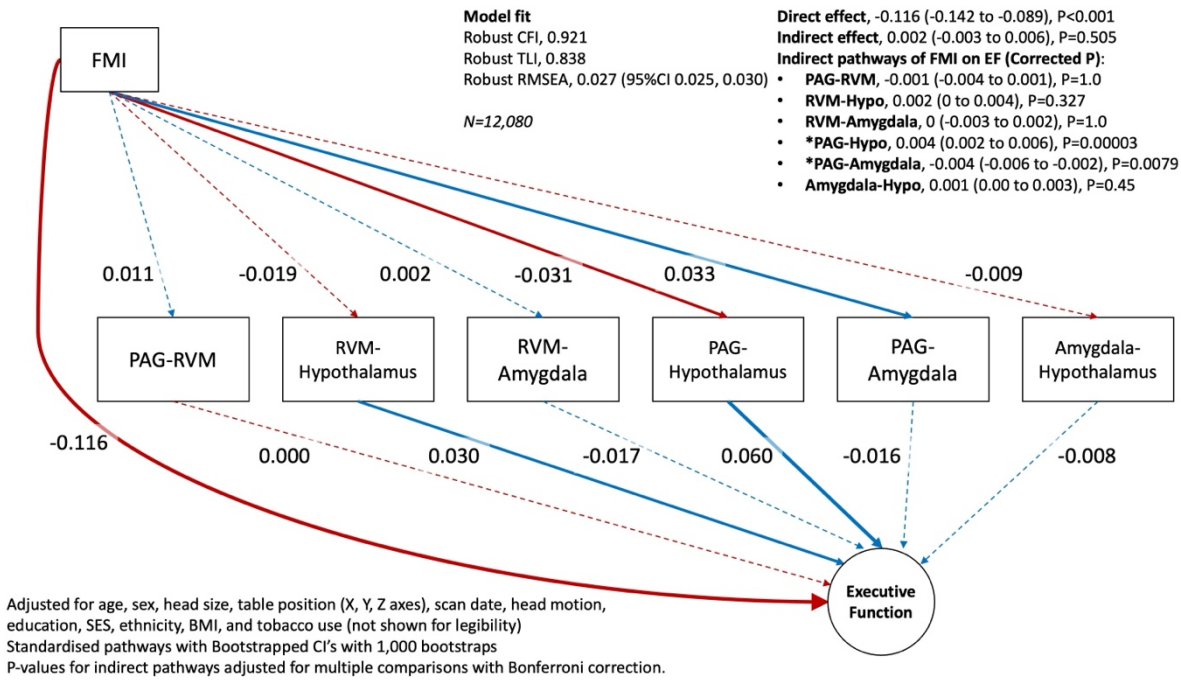


Figure 4-10. PAG-amygdala & PAG-hypothalamus structural connectivity mediates association with executive function in chronic pain.

Structural equation model of indirect effects of structural connectivity (SC) pathways within the descending pain modulatory system (DPMS) on the association between Fibromyalgia Index (FMI) score and executive function (EF) in adults with chronic pain (N=12,080).
Standardised parameter estimates are presented. Red lines indicate a negative association, while blue lines indicate a positive association. Solid lines represent significant paths, while dashed lines indicate non-significant relationships. Bootstrapped confidence intervals estimated with 5,000 iterations. Higher FMI scores indicate greater nociplastic pain severity, and lower EF scores indicate worse executive function. Significant pathways include PAG-Hypothalamus and PAG-Amygdala structural connectivity, while other pathways did not reach significance. Only the main pathways are displayed; indicators, exogenous confounders, and covariances between mediators are omitted for clarity. Model fit indices (CFI, TLI, RMSEA) and 95% confidence intervals (CIs) are provided in the figure. P-values for indirect pathways are adjusted for multiple comparisons with Bonferroni correction. PAG, periaqueductal grey; RVM, rostral ventromedial medulla; Amyg, amygdala; Hypo, hypothalamus.

4.3.6 Objective 4: Significant covariation between DPMS functional connectivity and biopsychosocial characteristics

Canonical correlation analysis (CCA) identified a significant mode of covariation between DPMS functional connectivity and biopsychosocial characteristics in 40,405 participants. The mean canonical correlation was r=0.062 (P=0.00126), indicating a subtle but statistically significant relationship (**Figure 4-11**). Key functional connectivity contributors included amygdala connections with the PAG, hypothalamus, rACC, and dlPFC, alongside the dlPFC-rACC connection (**Figure 4-12**).

Of biopsychosocial variables, self-reported sleep duration and neuroticism were the most influential variables driving this association (**Supplementary Figure C-5**). These findings align with prior evidence linking altered DPMS connectivity to sleep disruption and anxiety, underscoring the relevance of these traits to nociplastic pain mechanisms. Further exploration of these connections may illuminate pathways for targeted interventions in nociplastic pain.

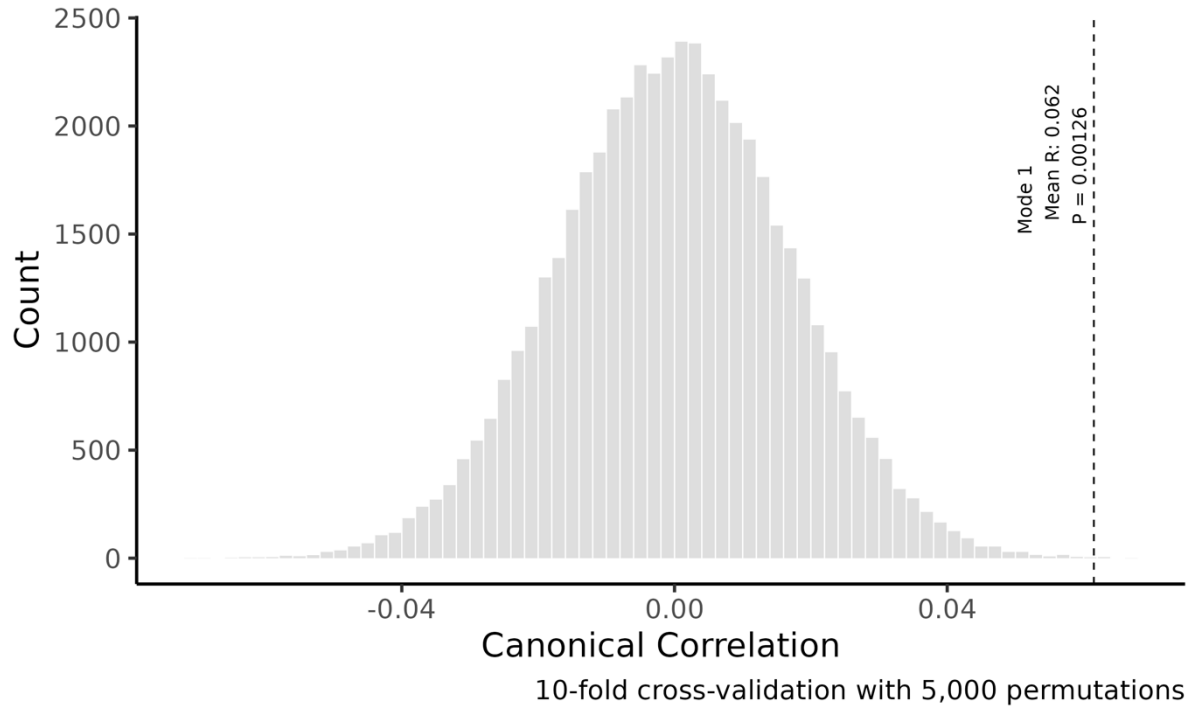


Figure 4-11. Significant mode of covariation between DPMS functional connectivity and biopsychosocial traits: permutation testing results

Canonical correlations and null permutation distribution for significant mode. The histogram represents the null distribution of canonical correlations obtained from 5,000 permutations of the outcome variables, serving as the null hypothesis of no association between the explanatory and outcome variables. The dashed vertical lines indicate the mean observed canonical correlations for the mode of covariation, overlaid for comparison with the null distribution. Annotated p-values reflect the statistical significance of the observed correlations, calculated as the proportion of permuted correlations exceeding the observed values.

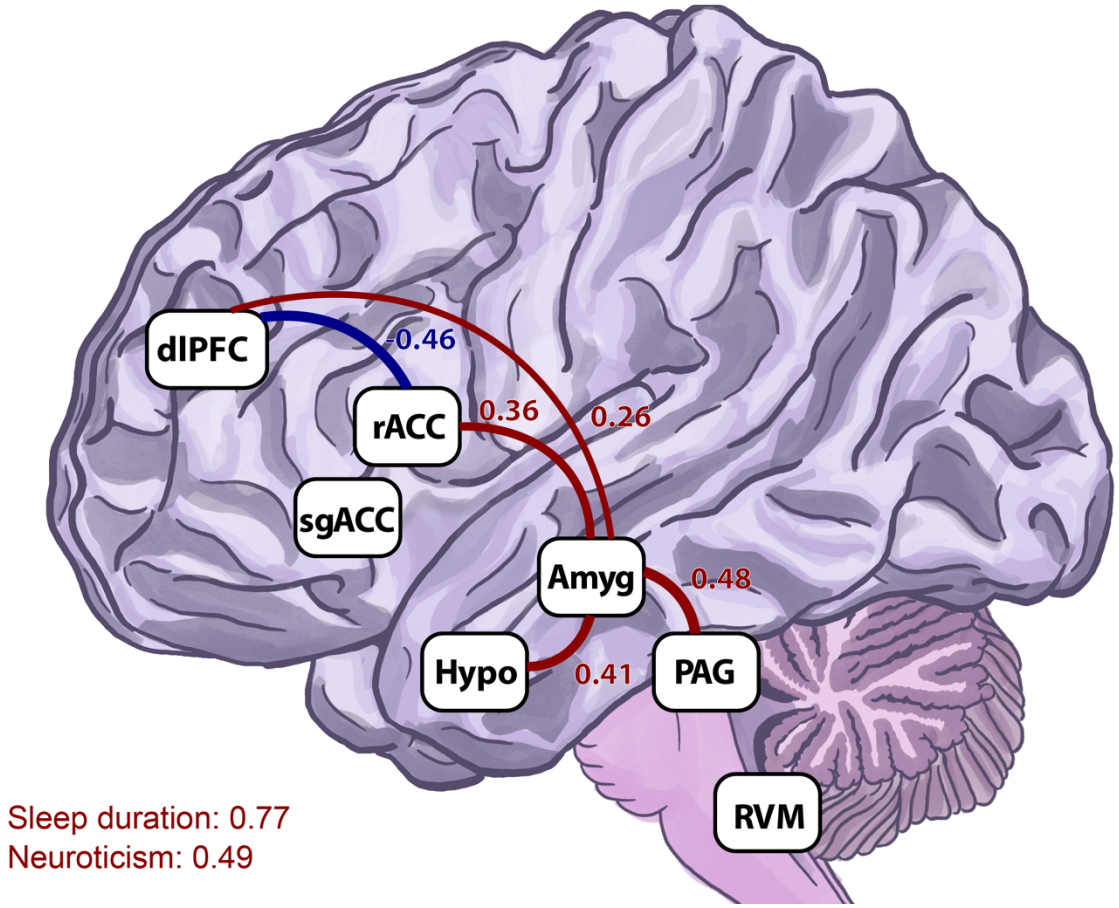


Figure 4-12. Amygdala-centred DPMS functional connectivity patterns linked to sleep and neuroticism traits

Brain connectivity patterns for significant mode of covariation. Mean correlation after cross-validation and P-value from permutation testing displayed. Lines illustrate RSFC connections with loadings ≥ |0.2| (red = positive; blue = negative). Nodes include the rostral ventromedial medulla (RVM), periaqueductal grey (PAG), hypothalamus (Hypo), amygdala (Amyg), rostral anterior cingulate cortex (rACC), subgenual anterior cingulate cortex (sgACC), and dorsolateral prefrontal cortex (dlPFC).

4.4 Discussion

4.4.1 Summary

In this chapter, I demonstrate that both functional and structural connectivity within the DPMS demonstrate a small, but significant, association with nociplastic pain severity, as measured by the FMI.

Structural connectivity within the DPMS displayed a relatively stronger association with nociplastic pain severity, which was only modestly attenuated after adjustment for sociodemographic and lifestyle confounders (**Figure 4-7**). Regarding individual pathways, stronger PAG-amygdala structural connectivity is associated with higher FMI scores, particularly in those with chronic pain. Weaker structural connectivity between the hypothalamus and both RVM and PAG are also associated with higher FMI. In addition, structural connectivity between the RVM and PAG displayed contrasting effects depending on chronic pain status; those with chronic pain who had higher RVM-PAG structural connectivity had higher FMI scores, while the inverse was observed in adults with lower RVM-PAG structural connectivity (**Figure 4-8**).

Functional connectivity in the DPMS explains a small portion of the variance in FMI, which was weaker than that observed for structural connectivity (**Figure 4-5**). In contrast to structural findings, the relationship between PAG-amygdala functional connectivity and FMI is non-linear, with both low and high functional connectivity associated with lower FMI scores. Unlike structural connectivity, chronic pain status does not significantly modify these functional relationships. For both structural and functional connections, the predominant pathways affecting FMI in this study involve

the brainstem and subcortical structures, such as the amygdala and hypothalamus, rather than cortical structures such as the dlPFC and ACC. This may be due to the relatively healthy status of UK Biobank participants, with changes to cortical connectivity appearing in those more adversely affected by chronic pain.

Additionally, both structural and functional connectivity, particularly in the PAG-amygdala and PAG-hypothalamus pathways, mediate a small but significant indirect relationship between nociplastic pain severity and executive dysfunction, with structural pathways playing a more substantial role (**Figure 4-9** & **Figure 4-10**). This adds to earlier findings from Chapter 3 that pain severity may play a role in the cross-sectional relationship between executive dysfunction and nociplastic pain.

Multivariate analysis highlights a significant pattern linking DPMS functional connectivity with biopsychosocial factors, particularly sleep disturbance and neuroticism, underscoring the interplay between neural circuits and the emotional and cognitive dimensions of chronic pain (**Figure 4-12**). However, the observed correlation was relatively weak (r=0.062).

Why were observed associations stronger for structural, rather than functional, connectivity? This may reflect the long-term, cumulative impact of chronic pain on neural pathways within the DPMS. Structural changes could represent acquired adaptations to prolonged pain exposure, manifesting as enduring neural reorganisation. These changes may be more behaviourally salient compared to functional connectivity, which captures dynamic, state-dependent interactions that

could fluctuate with momentary factors like arousal or emotional state. Methodological considerations, such as voxel resolution imaging acquisition parameters in UK Biobank, may also limit sensitivity to functional activity in subcortical regions like the PAG. Future longitudinal studies, incorporating repeated measures of pain severity and connectivity, are needed to disentangle biological and methodological explanations and to explore the temporal evolution of these structural and functional changes.

4.4.2 Descending Pain Modulation System

The DPMS serves a dual function in pain modulation, capable of both inhibiting and facilitating nociceptive processing depending on the context[27]. The PAG plays a pivotal role as a hub integrating top-down signals from cortical areas, such as the dlPFC and ACC, with bottom-up nociceptive input from the spinal cord[334]. Its role extends beyond pain modulation, encompassing autonomic responses and defensive behaviours[146; 150; 207; 452]. Evidence from neuroimaging studies suggests that this balance between facilitation and inhibition can become disrupted in chronic pain, leading to a pro-nociceptive state characterised by hypersensitivity and reduced pain inhibition[27; 334].

Structural and functional changes in PAG connectivity are well-documented in fibromyalgia and other chronic pain conditions[57; 91; 220; 360]. Tractography studies have shown that the PAG is connected to key DPMS regions, including the hypothalamus, amygdala and PFC[146]. In healthy adults, a RVM-PAG-ACC resting state network supports the functional integration of the DPMS[243]. In fibromyalgia, reduced RVM-PAG connectivity is associated with increased pain facilitation during

conditioned pain modulation (CPM), a suggested proxy for descending pain inhibition[190]. However, not all patients with fibromyalgia experience pain facilitation during CPM; some patients exhibit intact descending pain inhibition despite similar clinical symptoms, suggesting that impaired descending inhibition is one of multiple mechanisms contributing to fibromyalgia[357]. The present study found that PAG-amygdala connectivity was most strongly associated with nociplastic pain severity at a population-level. This aligns with evidence supporting the amygdala's role in the emotional and cognitive modulation of pain, serving as a relay between the PAG-RVM axis and higher cortical regions[188; 197]. These results suggest that the PAG-amygdala pathway may play an important role in mediating the affective and cognitive dimensions of nociplastic pain.

The amygdala is implicated in the fear response and anticipatory aspects of pain and may mediate the dysregulated affective control observed in fibromyalgia. Previous studies have reported reduced amygdala volume[67] and altered functional connectivity with other DPMS nodes, such as the ACC[221]. My CCA findings build on this by demonstrating that increased PAG-amygdala connectivity is associated with greater symptom severity and related biopsychosocial factors such as sleep disturbance and anxiety. These results are consistent with the known contributions of the amygdala to stress and arousal states, which exacerbate pain perception, supporting the notion that nociplastic pain is influenced by a complex interplay of biological, psychological, and social factors. This aligns with pain vulnerability models, which suggest that altered neural circuits may predispose individuals to chronic pain by amplifying the impact of psychosocial stressors[123]. The relatively stronger

association between PAG-amygdala connectivity and nociplastic pain severity, compared to PAG-RVM connectivity, may reflect the amygdala's unique role in integrating affective, cognitive, and autonomic dimensions of pain. Unlike the RVM, which is predominantly implicated in spinal nociceptive modulation, the amygdala is central to stress and emotional responses, both of which are known to amplify nociceptive processing. This heightened connectivity may represent a stress-pain feedback loop in which emotional dysregulation exacerbates pain perception, particularly in conditions such as fibromyalgia that are characterised by significant biopsychosocial comorbidities

Latent sensitisation provides a framework for understanding the transition from acute to chronic pain in the context of altered DPMS function, where there is a compensatory increase in descending inhibitory tone following injury, masking ongoing sensitisation. When this mechanism fails, unmasked hyperalgesia emerges, which may contribute to the persistence of chronic pain[82]. The observed changes in DPMS connectivity may reflect a similar exhaustion of compensatory inhibitory processes, resulting in the pro-nociceptive states associated with nociplastic pain. **Table 4-4** summarises the complex interplay between DPMS activity and pain response.

	Increased activity	Decreased activity
Facilitation (ON-cells)	↑ *pain*	↓ *pain*
Inhibition (OFF-cells)	↓ *pain*	↑ *pain*

Table 4-4. Interpreting DPMS Activity in Relation to Pain Perception

This table highlights the bidirectional modulation of pain by the descending pain modulatory system (DPMS) through its facilitation and inhibition mechanisms. Increased activity of DPMS facilitation neurons (ON-cells), such as those in the rostral ventromedial medulla (RVM) and periaqueductal grey (PAG), correlates with increased pain perception. Conversely, decreased activity of ON-cells reduces pain. For inhibitory neurons (OFF-cells), increased activity is associated with pain reduction, while decreased activity corresponds to enhanced pain. This dual role underscores

the complexity of interpreting DPMS imaging studies, as activity changes in either direction (facilitatory or inhibitory pathways) have opposing implications for pain outcomes.

4.4.3 Relationship between functional and structural connectivity

Structural connectivity provides the framework within which functional connections exist as brain network patterns depend on anatomically plausible pathways[121]. A landmark modelling study by Honey *et al.*[205] demonstrated that structural architecture constrains the range of possible functional interactions. While functional connectivity can occur between regions without direct anatomical connections via indirect or polysynaptic pathways, the presence of structural links increases the probability and strength of functional connectivity[205].

Across the brain, structurally connected regions are more likely to exhibit functional connectivity during both rest and task conditions[198]. Strong structural connections (e.g., interhemispheric tracts via the corpus callosum) typically support strong functional connectivity, while absent or disrupted structural connections result in weaker functional coupling. For instance, in individuals with congenital agenesis of the corpus callosum, interhemispheric functional connectivity is diminished during task fMRI[363]. Similarly, canonical resting-state networks tend to involve anatomically connected regions[205]. However, the absence of a direct tract does not preclude functional connectivity, which may arise through intermediate nodes[205].

While structural connectivity is relatively stable, functional connectivity is more variable over time. Nonetheless, structurally connected regions exhibit more consistent resting state functional connectivity than those that are unconnected[205]. This is observed in the DPMS, where white matter tracts connecting key nodes such as

the RVM, PAG, and ACC, support its function as an integrated network[188]. These regions also show functional co-activation, particularly during evoked pain.

In chronic pain, white matter connectivity may predict the risk of pain persistence. For example, in low back pain, white matter tract integrity between the nucleus accumbens and medial prefrontal cortex assessed prior to symptom onset predicted individuals who developed chronic pain from those who recovered[289]. Structural integrity also appears to support pain modulation; in healthy individuals, structural connectivity between the DLPFC and thalamus correlated with functional connectivity and analgesic response to tDCS[267]. Similarly, white matter integrity in PAG-ACC and PAG-DLPFC pathways is associated with placebo analgesia[431].

Although structural pathways provide the skeleton on which functional connections occur, the relationship between changes in structural and functional connectivity is bidirectional. Changes in functional activity can induce structural changes, as shown by studies where repeated co-activation induced by learning a visual task increases both functional coupling and white matter integrity between task-relevant areas[228]. Conversely, structural decline (e.g., age-related white matter loss) is associated with reduced functional connectivity in affected pathways[396]. Functional reorganisation may compensate for disrupted structure, allowing preserved function via alternative pathways, though such compensation may be limited or revealed only under challenge. This may explain why structural connectivity is more strongly associated with pain-related outcomes than resting-state functional measures in this study. It may be that evoked pain would better expose latent functional alterations.

In summary, structural connectivity provides the anatomical scaffold for functional connections. However, this scaffold is modifiable, and changes in functional dynamics

over time can sculpt structural connectivity. This structure-function coupling varies by brain region and context, with tighter coupling observed in certain networks such as the salience and dorsal attention networks[274].

4.4.4 Role in executive dysfunction

The association between PAG-amygdala connectivity and executive function highlights a novel link between descending pain modulation and higher-order cognitive processes, although the effect sizes observed in this study are modest. This finding extends the existing literature by demonstrating that alterations in DPMS connectivity are associated not only with nociplastic pain severity but also cognitive impairments frequently reported in these conditions. The PAG modulates higher cortical control of pain through attentional mechanisms; distraction and other cognitive strategies influence PAG activity in response to nociceptive stimuli[452; 459]. Recent neuroimaging studies have demonstrated that attentional analgesia, where pain perception is attenuated through distraction, is mediated by a pathway involving the PAG, RVM, and ACC[344]. This pathway supresses activation in the spinal cord, and is blocked by naltrexone, an opioid antagonist, highlighting the role of endogenous opioids in the DPMS[345]. Disruption of this modulation in chronic pain conditions may impair executive functions such as attentional flexibility, contributing to the cognitive deficits commonly reported in fibromyalgia. The findings in this chapter suggest a dual functionality of the PAG, linking nociceptive modulation with executive function, and situating DPMS disruptions within a broader framework of impaired cognitive control mechanisms in chronic pain.

Altered PAG connectivity may also reflect a reduced ability to engage top-down cognitive control mechanisms in response to pain, contributing to cognitive deficits. This aligns with findings in patients with multiple sclerosis-related chronic neuropathic pain, where reduced rACC to ventrolateral PAG connectivity was associated with increased pain perception, suggesting this pathway plays a role in descending pain inhibition, which may be associated with the impaired executive function observed in this group[161]. These results also build on findings in Chapter 3 (Section 3.3.6.2), where pain intensity mediated an indirect pathway between FMI and executive function. Interestingly, the apparent intactness of attentional modulation in fibromyalgia reported in a recent study might reflect compensatory engagement of alternate DPMS pathways or context-specific demands[343]. Differential recruitment of the PAG during attentional analgesia suggests a nuanced role that may vary across chronic pain conditions.

4.4.5 Strengths & limitations

This principal strength of this study is the large population-based sample size of over 40,000 adults with neuroimaging data. This allows the detection of even small associations between DPMS connectivity and pain characteristics. The multimodal approach – utilising both functional and structural neuroimaging – reinforces the findings, with the same key characteristic (PAG-amygdala connectivity), appearing in both analyses. By employing both univariate approaches such as GAM, and multivariate approaches such as CCA, the study aimed to evaluate both depth and breadth. The univariate results pinpoint specific relationships for further evaluation,

such as the PAG-amygdala relationship, while CCA contextualises these relationships within a multivariate framework, suggesting the relationship between wider amygdala connectivity patterns with traits such as neuroticism and sleep disturbance. Together, these methods present a case for a multidimensional, systems-level approach to understanding nociplastic pain.

While this study provides evidence for the nature of the involvement of the DPMS in nociplastic pain, several limitations must be acknowledged. First, this is a cross-sectional study, and the direction of association between connectivity measures and pain cannot be deduced. Although the large sample size is a strength, it may allow the detection of small effects of little clinical relevance. However, these are beneficial to improving our understanding of the underlying neurobiology of nociplastic pain, and guiding future targeted studies in clinical populations. Furthermore, the neuroimaging sequences used in UK Biobank were not optimised for brainstem structures, potentially introducing noise into PAG and RVM measurements. Although resting-state functional connectivity can predict behaviour and activations during task fMRI[100; 421; 524], it may be relatively insensitive to changes in the DPMS. Future studies evaluating evoked pain during fMRI acquisition may be more sensitive to interrogating the nature of DPMS disruption in chronic pain. Additionally, the reliance on indirect measures of DPMS function, such as resting-state functional connectivity, limits the ability to distinguish between facilitation and inhibition. It is important to note that the interpretation of BOLD activity in PAG-amygdala connectivity as either pro-nociceptive or anti-nociceptive remains challenging due to the limitations of resting-state neuroimaging in distinguishing between facilitation and inhibition within the DPMS (**Table 4-4**). Future

studies employing task-based fMRI paradigms or pharmacological manipulations targeting the PAG-amygdala circuit are needed to disentangle these mechanisms and clarify their functional implications in nociplastic pain. This study is also limited by the selection of both neuroimaging and behavioural variables, and by the definition of the ROI masks. Replication of these findings in independent datasets using independent masks would reinforce the observed associations. QST measures evaluating DPMS function, such as CPM and temporal summation, were not performed in UK Biobank, although findings from these techniques have not been very reproducible[330].

4.4.6 Conclusion

Understanding the role of PAG-amygdala connectivity in nociplastic pain opens potential avenues for targeted therapeutic interventions, such as neuromodulation or pharmacological strategies aimed at restoring balance within this circuit. Such approaches could address not only the sensory dimensions of pain but also the emotional dysregulation and stress-related mechanisms that are prominent in conditions like fibromyalgia, ultimately improving both pain and associated biopsychosocial symptoms.

In conclusion, this chapter highlights the important role of DPMS connectivity, particularly the PAG-amygdala pathway, in nociplastic pain severity at a population-level and its associated emotional and cognitive dimensions. Future longitudinal studies should evaluate whether these changes precede nociplastic pain, suggesting a pre-existing vulnerability to pain. These findings complement existing evidence of DPMS

dysfunction in chronic pain and underscore the need for targeted studies evaluating the DPMS in relation to cognitive and emotional features in nociplastic pain conditions such as fibromyalgia.

5 Chapter Five: PainLESS Study: a feasibility randomised trial of dCBT-I nested in an observational study of musculoskeletal pain

5.1 Introduction

Fibromyalgia is a debilitating and poorly understood condition characterised by chronic widespread pain, fatigue, cognitive impairment, and sleep disturbance. Affecting approximately 5% of the UK population, fibromyalgia imposes a significant socioeconomic burden, with many patients experiencing reduced productivity and increased reliance on healthcare services[152; 399; 425]. Within five years of diagnosis, 25% of fibromyalgia patients are unable to work, underscoring the need for effective interventions[425; 427].

Sleep disturbance is a hallmark feature of fibromyalgia, reported by up to 90% of patients, and it significantly impacts quality of life, pain management, and cognitive functioning ("fibrofog")[88; 94]. This vicious cycle between disrupted sleep, pain, and cognitive dysfunction diminishes quality of life and functional capacity[88; 94]. Despite its near-universal presence in fibromyalgia, sleep dysfunction remains relatively under investigated as a therapeutic target, and accessible, scalable treatment options are lacking.

Patient priorities, as outlined by the James Lind Alliance and recent NICE guidelines (NG193[2]), have emphasised the need to develop and evaluate sleep interventions in chronic pain populations[158].

Cognitive Behavioural Therapy for Insomnia (CBT-I) is the gold-standard non-pharmacological treatment for chronic insomnia, with robust evidence supporting its efficacy in improving sleep quality and quality of life[367]. Beyond its benefits for sleep, CBT-I has shown potential for addressing pain, fatigue, and cognitive symptoms in chronic pain conditions (see Chapter 2)[253; 393; 443]. However, conventional face-to-face CBT-I often faces logistical and financial barriers, limiting its accessibility for fibromyalgia patients. Digital CBT-I (dCBT-I), delivered via online platforms, offers a scalable, cost-effective alternative, with evidence demonstrating comparable efficacy to in-person therapy[516].

Despite its promise, the application of dCBT-I in fibromyalgia is underexplored. Several pilot studies in other chronic pain conditions, such as osteoarthritis and migraine, suggest potential benefits, but large-scale trials in fibromyalgia are lacking[109; 488]. Moreover, the mechanisms by which dCBT-I may improve sleep and quality of life in fibromyalgia, and alleviate symptoms such as cognitive dysfunction, remain unclear. This research gap highlights an opportunity to evaluate the feasibility and impact of dCBT-I in fibromyalgia and to explore its underlying mechanisms.

In this study, I aim to address these gaps by conducting a feasibility trial of dCBT-I, delivered via the *Sleepio*, in patients with fibromyalgia. In addition to evaluating recruitment, retention, and engagement, the study examines a comprehensive range of outcomes, including quality of life, sleep quality, cognitive performance, and neuroimaging measures. By embedding the trial within a larger observational cohort, the study aligns with real-world clinical settings and ensures efficient data utilisation[239].

Designed in collaboration with fibromyalgia patients, this study incorporates patient-centred priorities, such as addressing fibrofog and using digital delivery to overcome barriers to face-to-face therapy. If feasible, this trial will pave the way for a fully-powered RCT to evaluate the efficacy and mechanisms of dCBT-I in fibromyalgia, contributing to the development of accessible, evidence-based treatments for this underserved population.

5.1.1 Aims and Objectives

- **Aim:** To assess the feasibility of a trial evaluating digital Cognitive Behavioural Therapy for Insomnia (dCBT-I) delivered via *Sleepio* on quality of life, sleep quality, and cognitive function, with a neuroimaging sub-study, in fibromyalgia patients.
- **Objective:** To evaluate recruitment, retention, and engagement rates, and estimate the required sample size for a future randomised controlled trial.

5.2 Methods

5.2.1 Overview of trial design

This study aimed to evaluate the feasibility of conducting a RCT assessing the effectiveness of digital cognitive behavioural therapy for insomnia (dCBT-I) using the *Sleepio* program, compared with standard sleep hygiene advice, in patients with fibromyalgia.

The feasibility trial was nested within a larger prospective cohort study titled *'Characterisation of **Pain** in Patients with Musculoskeletal Disease: A **L**ongitudinal, Observational Study with an **E**mbedded Feasibility Window of Opportunity **S**leep **S**tudy*' (**PainLESS**). This parent cohort provided a robust foundation for examining sleep, cognition and pain-related outcomes in fibromyalgia. Eligible patients in the observational study were invited to take part in the feasibility trial.

The trial was designed to maximise feasibility in a chronic pain population[235], with fibromyalgia chosen as the population of interest due to the high prevalence of sleep disturbances[88]. To enhance eligibility and ease of implementation, exclusion criteria were kept to a minimum, and the screening process was streamlined. This approach aimed to improve generalisability to real-world clinical settings, where extensive screening is often impractical. Based on work with Public and Patient Involvement and Engagement (PPIE) groups, the trial was designed to utilise remote, computer-based, assessment tools where possible, with automated reminders to complete assessments to maximise retention rates.

The study received ethical approval from South Central – Oxford B Research Ethics Committee (ref: **19/SC/0168**; IRAS Project ID **25276**), and was pre-registered with clinicaltrials.gov (ref: **NCT05962138**). The interim feasibility analysis was conducted without unblinding after 30 participants were randomised. As funding was obtained to continue the trial based on the results of the interim feasibility analysis, the trial was not unblinded. Thus, the blinded feasibility outcomes are presented here. Analyses of baseline data from the latest data available (as of September 2024) are presented in Chapter 6.

5.2.2 Interventions - *Sleepio*

Sleepio is a dCBT-I programme, delivered online over 12 weeks, which has been demonstrated to improve sleep quality and subjective cognitive difficulties in insomnia[141; 253].

Sleepio was developed by Colin Espie of the University of Oxford, and Peter Hames, an insomnia patient, who co-founded *Big Health* to develop the program. *Sleepio* consists of six one-hour sessions with an animated virtual therapist ("The Prof") covering key cognitive and behavioural strategies to improve sleep (**Table 5-1**)[141]. The program is delivered in a web application, which can be accessed on mobile devices or a desktop computer, and the content is guided by the participants' baseline sleep characteristics, adherence to treatment, performance, and change of sleep behaviour during the treatment period. At the beginning of each session, the participant reviewed their sleep

diary information and current sleep patterns with the virtual therapist. *Sleepio's* algorithm allowed the content to then be tailored for each participant.

The content of *Sleepio* followed core CBTi principles, and included cognitive (e.g. thought re-structuring, mindfulness) and behavioural (e.g. sleep restriction therapy and stimulus control) components, in addition to relaxation techniques (e.g. progressive muscle relaxation). The key component of CBTi is thought to be 'sleep restriction therapy', where patients are initially instructed to limit their time in bed to match their sleep duration, before slowly relaxing this over time to increase sleep duration and efficiency. This was delivered in session three, where the virtual therapist proposes a new sleep window for a participant based on their sleep diary data, and helps them choose an appropriate time window for this from a set of options.

Sleepio has demonstrated efficacy for improving sleep quality in RCTs of primary insomnia[141]. It has also been shown to improve workplace productivity[58], measures of anxiety and depression[84; 301], paranoia and hallucinations[165], psychological wellbeing and sleep-related quality of life[139]. Of particular interest to the present study, *Sleepio* has also demonstrated efficacy at improving subjective cognitive symptoms in patients with insomnia, although there was no benefit to performance on a set of cognitive tests adopted from UK Biobank[253].

At the time the PainLESS study was commenced, *Sleepio* was available nationally in Scotland, but not in England. As of August 2024, it is available on the NHS in the Frimley and Buckinghamshire, Oxfordshire, and Berkshire West Integrated Care System (ICS) regions. *Big Health* provided access to *Sleepio* for participants in the PainLESS study at no charge. *Big Health* played no role in the design or conduct of the study, or in any analyses. Participants who have accessed *Sleepio* through the NHS or other studies

were not eligible for the PainLESS study. Participants who were randomised to Sleepio received an email with a code to access the programme. Common access issues, such as login difficulties or browser compatibility, were addressed through a troubleshooting guide. All trial participants received evidence-based sleep hygiene advice from the *Versus Arthritis* patient information booklet on fibromyalgia (available from: [19]). This constituted the standard care (control) arm.

Session	Description
1	Formulation, goal setting, sleep diary
2	Sleep hygiene, progressive relaxation, thought checker
3	Sleep hygiene (scheduling), stimulus control, sleep restriction
4	Cognitive restructuring, autogenic training, imagery, mindfulness, paradoxical intention (*session content tailored to individual priorities*)
5	
6	Review sleep goals and reinforce motivation

Table 5-1. Overview of sessions in Sleepio. Sessions were delivered over a minimum of six weeks (maximum ten weeks). The program is fully online, and is delivered by a virtual therapist ("The Prof").

5.2.3 Recruitment and Screening

Patients with fibromyalgia from OUH NHS trust or Connect Health (a clinical stakeholder organisation with responsibility to assess and manage patients with musculoskeletal conditions in the NHS in Oxfordshire) were invited to participate in the trial alongside their routine care of fibromyalgia. Information about the trial was disseminated at local departmental meetings, with clinicians encouraged to mention the trial to potentially suitable candidates. Additionally, patients referred to the Optimise pain management programme at OUH were directly contacted with trial details and invited to participate. Patients with fibromyalgia who were part of an existing musculoskeletal pain observational cohort study were also invited to participate in this

sub-study. The trial was also advertised across multiple settings, including the pain management centre, rheumatology outpatient clinics, and Connect Health clinics (see Appendix D, Section D.1). The trial was also listed on the NIHR online research portfolio, allowing interested patients to contact the research team directly via a dedicated email address (fibromyalgia@ndcn.ox.ac.uk). The eligibility criteria are summarised in **Table 5-2.**

Interested patients were sent a copy of the participant by email (see Appendix D, Section D.2) and were invited to complete an online screening questionnaire on Microsoft Forms. During a follow-up phone call, eligibility was confirmed, and patients had the opportunity to ask questions about the trial. For patients willing to undergo brain MRI, a detailed MRI safety screening was conducted to assess eligibility for this sub-study (see Appendix D, Section D.4).

Inclusion criteria	Exclusion criteria
Aged 18 years or older	Major neuropsychiatric condition (excluding depression and anxiety)
Meets 2016 American College of Rheumatology diagnostic criteria for fibromyalgia[499]	Diagnosis of neurological condition which could affect pain or cognitive assessment (e.g. Parkinson's disease, Dementia, cognitive impairment, or other neurodegenerative disorders)
Self-reported difficulties with concentration or memory in the Daytime Functioning and Sleep Attribution Scale (DFSAS) [254]. Individuals who reported "*quite a bit*" or "*very much*" trouble on at least one of concentrating or focusing on things were eligible.	Epilepsy (which may be worsened by sleep restriction therapy)
Insomnia, frequent waking, or early morning waking on 2-item Sleep Condition Indicator (SCI-2) [140]. Individuals who reported problems sleeping *at least 3 nights per week* and who reported that poor sleep troubled them "*much*" or "*very much*" were eligible.	Recent (<6 weeks) or planned surgery during trial period
Access to a device with a reliable internet connection (e.g. smartphone, tablet, computer)	Current or planned nightshift work during trial period (>1 per week)
Ability to read and understand English	Other untreated sleep disorder (e.g. obstructive sleep apnoea, restless leg syndrome, circadian rhythm disorder, parasomnia) [497]
Willing and able to provide informed consent for participation	Taking prescribed sedative sleep medications on >2 nights in the past 2 weeks prior to study entry
	Currently receiving other psychological therapy for insomnia
	Currently pregnant or breastfeeding
	For participants in the neuroimaging sub-study, additional exclusion criteria included any contraindication to MRI, including claustrophobia, certain metal implants, or other medical devices

Table 5-2. Eligibility criteria for feasibility trial of Sleepio in fibromyalgia.

Note: contra-indication to MRI is an exclusion criterion only for neuroimaging sub-study.

5.2.4 Informed consent

Informed consent was obtained remotely via telephone, and a copy of the signed consent form was sent to the participant via email (see Appendix D, Section D.3). A

hard copy was printed and stored in the trial master file, and was shown to the participant when they attended the trial visit. A copy was also scanned into the participant's electronic health record by a research nurse.

During this phone call, a date and time was arranged for the baseline trial visit. One week prior to this visit, participants received an email with instructions how to complete the online assessments (described in Section 5.2.6.1).

5.2.5 Randomisation, Allocation Concealment & Blinding

Following completion of all baseline assessments, participants were randomised on a 1:1 basis using *Sealed Envelope,* a secure electronic randomisation platform. To ensure balanced group allocation, randomisation was stratified by sex and participation in the neuroimaging sub study (see Section 5.2.7.5), with participants assigned in blocks of 10.

To maintain allocation concealment, I did not have access to future group allocations and was unable to influence randomisation. The treatment allocation was communicated to participants by an independent research nurse (MM & JD) via email. This email consisted of scripted phrases and contained instructions for *Sleepio* access. In addition, the research nurse acted as an intermediary for any queries regarding the treatment or group allocation, and relayed questions to me anonymously.

Due to the nature of the intervention, blinding participants was not possible. However, I remained blinded to treatment allocation throughout the trial. Participants were instructed not to disclose their group assignment to me during follow-up visits to maintain blinding.

5.2.6 Data collection

A number of behavioural and imaging measures were collected at baseline and during follow-up. A cross-sectional analysis of the baseline values of these variables is described in Chapter 6. The pre-registered primary clinical outcome for the trial is disease-related quality of life at 12 weeks, as measured by the Revised Fibromyalgia Impact Questionnaire (FIQR)[43]. Secondary outcomes include subjective and objective cognitive function, pain ratings, self-reported sleep quality, and sleep quality. Neuroimaging outcomes will also be collected in a sub-group of participants. An overview of these assessments is provided in the next section (5.2.6.1).

5.2.6.1 Trial visits and assessments

An overview of the feasibility trial design is given in **Figure 5-1**. In brief, prior to randomisation, participants completed a series of home-based assessments before attending a baseline visit in FMRIB, Oxford. There were follow-up assessments at 12-, 24-, and 52-weeks post-randomisation. The 12-week assessment included a repeat visit to FMRIB in addition to the online assessment, while the 24- and 52-week assessments were online only. Participation in the neuroimaging component and focus group were optional. Participants were reimbursed for the cost of their travel and parking.

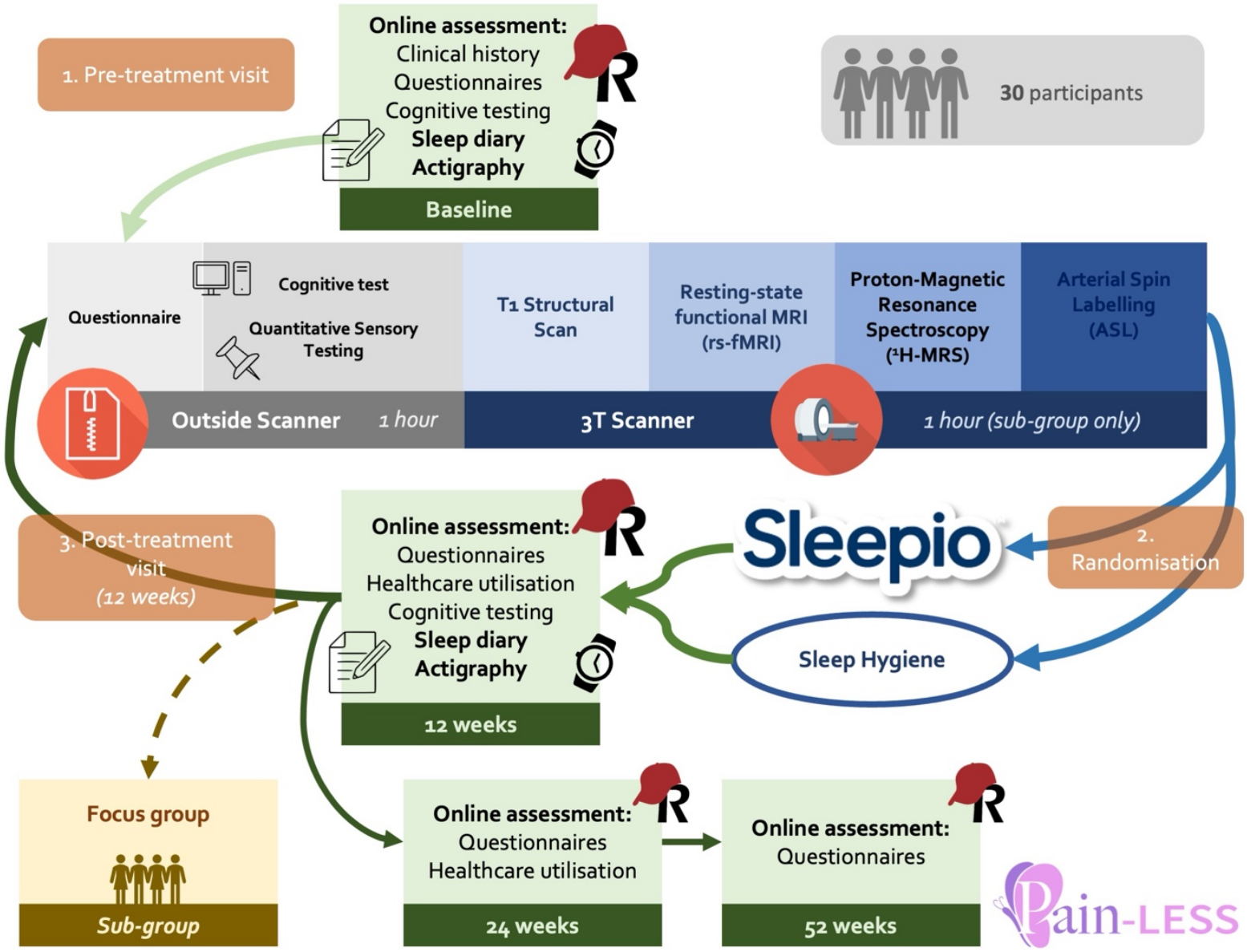


Figure 5-1. Overview of feasibility study design.

The post-treatment assessment at 12-weeks involved an online assessment and repeat in-person visit. The 24- and 52-week assessments were online only. Participants were randomised only when all baseline assessments were completed. Participants who completed the 12-week post-treatment assessment were invited to take part in a focus group, which was conducted in July 2024. All study visits took place in the Oxford Centre for Functional MRI of the Brain (FMRIB), John Radcliffe Hospital

5.2.6.1.1 Baseline assessment

Prior to the baseline trial visit, participants completed a series of online home-based assessments. These included a questionnaire collecting information on socio-demographics, relevant medical history, medication use, pain, sleep, cognition, and mental health. This was carried out using REDCap, a secure web application. The online questionnaire underwent several rounds of testing before being made live to minimise any errors and to ensure accuracy and integrity of the data collection. In addition, participants completed a series of online cognitive tests which evaluated domains including working memory, concentration and attention. These were developed by colleagues at the Department of Experimental Psychology in Oxford (SZ)[520].

At the baseline visit in FMRIB, participants underwent a range of assessments including quantitative sensory testing (QST), quantitative motion testing (QMT), completed a test of sustained attention (number vigilance task, NVT), had a blood sample taken, and underwent neuroimaging. At the end of the visit, participants were given an actigraphy watch (CamNtech MotionWatch 8) to wear for seven days, which tracked sleep and physical activity. They were asked to maintain the Consensus Sleep Diary[73] during this period.

For the purposes of my DPhil, the key assessments examined were fibromyalgia-related quality of life (FIQR), subjective cognitive difficulties (BC-CCI), sleep quality (ISI & PSQI), and sustained attention on the NVT, and resting state fMRI. These are outlined in more detail in Chapter 6 (Section 6.2.2.1).

5.2.6.1.2 Post-treatment assessments

Following the treatment period, participants repeated the same set of online home-based assessments and a repeat in-person assessment, mirroring the baseline evaluations. This follow-up visit occurred between 10 and 14 weeks after randomisation, depending on participant availability. In addition, participants completed the online questionnaire 24- and 52-weeks following randomisation.

5.2.6.1.3 Focus group

A focus group on a subset of participants who completed the post-treatment assessment was conducted online to obtain qualitative information about feasibility of the intervention and trial design.

5.2.7 Trial outcomes

5.2.7.1 Questionnaires

Participants completed a series of validated questionnaires assessing pain, medical history, cognition, sleep, mood, physical activity, and quality of life. Given the close relationship between pain, mood, and anxiety, several measures of emotional well-being were included. An overview of the questionnaires collected in the study is given in **Table 5-3**.

Instrument	Score (direction)	Purpose
Demographics		Age, sex, handedness, ethnicity, employment status, education
Lifestyle		Alcohol use, tobacco use, height, weight
Medical history		Fibromyalgia symptom duration, fibromyalgia date of diagnosis, current and previous treatments including those for pain management specifically, analgesia use, and other medical co-morbidities
Pain Numeric Rating Scale (NRS)	0-10 (higher scores indicate worse pain)	To measure pain intensity
Fibromyalgia Impact Questionnaire Revised (FIQR)	0-100 (higher scores indicate worse quality of life)	To assess the overall impact of symptoms and quality of life in those with fibromyalgia
Fibromyalgia survey criteria	0-31 (higher scores indicate worse symptom severity)	To confirm fibromyalgia diagnosis and assess symptom severity
PainDETECT questionnaire	0-38 (higher scores indicate more likely neuropathic pain)	To assess for features and severity of neuropathic pain
Central sensitivity inventory (CSI)	0-100 (higher scores indicate more likely central sensitisation)	To assess for features of central sensitisation
Pain Catastrophising Scale (PCS)	0-52 (higher scores indicate greater catastrophising)	To assess for negative thoughts and feelings regarding pain
Chronic Pain Acceptance Questionnaire (CPAQ)	0-120 (higher scores indicate greater levels of acceptance)	To assess acceptance of pain symptoms
British Columbia Cognitive Complaints Inventory (BC-CCI)	0-18 (higher scores indicate greater cognitive symptom severity)	To assess self-reported cognition
Insomnia Severity Index (ISI)	0-28 (higher scores indicate greater insomnia symptom severity)	To assess severity of insomnia symptoms
Pittsburgh Sleep Quality Index (PSQI)	0-21 (total score, where higher scores indicate worse sleep quality). In addition, 7 component scores are derived including sleep duration and efficiency.	To assess sleep quality and patterns
Chalder Fatigue Scale	0-33 (Higher scores indicate greater fatigue)	To assess self-reported physical and mental fatigue severity
Tampa Scale for Kinesiophobia (TSK)	17-68 (Higher scores indicate greater fear of movement)	To assess fear of movement which may impact response to treatment
International Physical Activity Questionnaire (IPAQ) short form	MET-minutes or categorical score (inactive, minimally active, high active)	A measure of self-reported physical activity levels in the previous seven days

Instrument	Score (direction)	Purpose
Short Form 36 Health Survey (SF-36) Bodily Pain Scale	0-100 (Higher scores indicate less bodily pain)	To assess overall health and wellbeing
Behavioural Inhibition System/Behavioural Activation System (BIS/BAS) scale	BIS/Punishment Sensitivity, 5-20 (higher scores indicate greater punishment sensitivity). BAS, 12-52 (higher fun-seeking behaviour)	To assess punishment sensitivity and reward responsiveness which may be impaired in chronic pain and impact on treatment responsiveness
Patient Health Questionnaire 9 (PHQ-9)	0-27 (Higher scores indicate more severe depression symptoms)	To assess and describe depression and its impact on symptoms and treatment response
General Anxiety Disorder scale 7 (GAD-7)	0-21 (Higher scores indicate more severe anxiety symptoms)	To assess and describe anxiety and its impact on symptoms and treatment response
Euroqol-5D-5L (EQ5D5L)	-0.59-1.0 (Higher scores indicate better health states). EQ-VAS, 0-100 (Higher scores indicate better health states)	Standardised measure of health-related quality of life
Healthcare resource utilisation		To facilitate economic evaluation in conjunction with EuroQoL 5D 5L

Table 5-3. Overview of all questionnaires used in the trial.

Participants will be asked to complete all questionnaires at baseline and at 12-weeks, 24-weeks, and 52-weeks follow-up post-randomisation. A description of all questionnaires is given in the appendix D, Section D.5.

5.2.7.1.1 Demographics and medical history

Demographic information collected included age, sex assigned at birth, self-reported ethnicity, educational attainment (years in full-time education, and highest educational qualification), and employment status. Medical history encompassed the duration of fibromyalgia symptoms, the date of diagnosis (to the nearest month/year), current and previous treatments for fibromyalgia, and other medical conditions.

During the in-person assessment, participants were asked about current use of specific analgesic medications commonly used in fibromyalgia, including paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, amitriptyline, gabapentin or

pregabalin, and duloxetine. These medications are frequently prescribed to manage fibromyalgia-related pain due to their varied mechanisms of action. Space was also provided to enter free text for drugs not in that list, and participants were also asked how many hours previously they had last taken a dose. Participants rated how much pain relief analgesia medications provided on a scale of 0 (no relief) to 100 (complete relief).

Understanding participants' medical history, especially analgesia use, is important for assessing their potential confounding or mediating factors related to medication use that may influence pain perception or cognitive function[326].
Lifestyle factors such as alcohol and tobacco use were recorded. Additionally, height and weight were measured during the baseline trial visit.

5.2.7.1.2 Pain-related questionnaires

5.2.7.1.2.1 Fibromyalgia Impact Questionnaire Revised (FIQR)

The FIQR served as the primary clinical endpoint of the trial. It is a validated tool based on the revised symptom impact questionnaire (SIQR) used in rheumatology, and assesses the impact of fibromyalgia on an individual’s daily life[43]. It includes questions on the following domains: physical functioning, pain intensity and characteristics, fatigue, sleep quality, emotional well-being (mood and anxiety), and impact on work and social interactions.

5.2.7.1.2.1.1 Fibromyalgia Survey Criteria

The 2016 American College of Rheumatology fibromyalgia Survey Criteria is a set of diagnostic guidelines for fibromyalgia[499]. It consists of two domains, the symptom severity scale (SSS, 0-12), and widespread pain index (WPI, 0-19). The SSS evaluates severity of key symptoms in fibromyalgia, including poor sleep, brain-fog, fatigue, low mood, and somatic symptoms such as headaches and abdominal pain. The WPI measures self-reported pain in a set of 19 specific body regions where has been experienced in the past week. The WPI and SSS not only confirm fibromyalgia diagnosis but also provide a framework for measuring the intensity and distribution of nociplastic pain, a key mechanism in fibromyalgia. These metrics serve as both diagnostic tools and indicators of disease progression[230; 502].

5.2.7.1.3 Health-related quality of life

5.2.7.1.3.1 Short-form 36 Health Survey

The SF-36 health survey assesses overall health and wellbeing across eight domains[163]: physical functioning, role limitations due to physical health, role limitations due to emotional wellbeing, fatigue, emotional wellbeing, social functioning, pain, and general health. In this trial, the Bodily Pain subscale (BPS) is used as a measure of the impact of pain on physical health. It is a composite of two items measuring pain intensity and pain interference, a measure of how much pain interferes with daily activities. Scores for each subscale are transformed to a scale of 0-100, with lower scores representing worse health status.

5.2.7.1.4 Brain-fog

5.2.7.1.4.1 British Columbia Cognitive Complaints Inventory (BC-CCI)

The BC-CCI assesses subjective cognitive complaints through six items assessing self-reported problems over the past seven days with concentration, memory, expressing thoughts, word finding, thinking speed, and problem-solving[214]. Although more typically used in evaluation of patients with mood disorders, this outcome measure was selected for this trial to facilitate comparison with the SPIN trial, which evaluated the effect of dCBT-I on cognitive function in patients with insomnia[253].

5.2.7.1.5 Sleep quality

5.2.7.1.5.1 Insomnia Severity Index (ISI)

The ISI assesses severity of insomnia symptoms and their impact, and is a widely used measure of insomnia severity in both clinical and research settings[31; 81]. It consists of seven items evaluating different aspects of insomnia, including difficulties with falling asleep, staying asleep, and waking up early; satisfaction with current sleep patterns; interference with daily functioning; quality of life; worry about sleep problems. It may be a more valid measure of sleep quality changes with CBTi compared to the PSQI (Section 5.2.7.1.5.2)[81].

5.2.7.1.5.2 Pittsburgh Sleep Quality Index (PSQI)

The PSQI assesses sleep quality and patterns. It complements the ISI by providing an assessment of sleep quality across seven components: sleep quality, sleep latency,

sleep duration, sleep efficiency, sleep disturbance, daytime dysfunction, and use of sleep medications[69].

5.2.7.1.6 Other questionnaires

5.2.7.1.6.1 Patient Health Questionnaire 9 (PHQ-9)

The PHQ-9 is a widely used screening tool for depression, consisting of nine items corresponding to the diagnostic criteria for major depressive disorder[248]. The score on the questionnaire is a measure of depression symptom severity.

5.2.7.1.6.2 General Anxiety Disorder 7 (GAD-7)

The GAD-7 is a common tool used to screen for anxiety symptoms, consisting of seven items relating to the core anxiety symptoms including feeling nervous, inability to stop worrying, and difficulty relaxing[430]. The total score provides a measure of anxiety symptom severity.

5.2.7.1.6.3 Adverse events

At follow-up, participants reported any potential adverse events related to dCBT-I, including physical and psychological symptoms such as fatigue, low mood, pain, and difficulty concentrating. They rated the severity of these symptoms and how much they interfered with normal functioning, on a scale from "Did not experience" to "Very much." Participants also reported incidents of sleepiness over the preceding 3 months,

including hospital admissions, accidents, falls, or near-miss incidents, and had the opportunity to mention any other relevant events.

5.2.7.1.7 Healthcare resource utilisation

For a planned economic evaluation, participants reported their healthcare service use over the previous 3 months, including hospital visits, medical imaging, and consultations with healthcare professionals (e.g., GPs, nurses, physiotherapists). Information was also collected on medications, unpaid caregiving, social services, and the financial impact of the condition on relatives and friends, including out-of-pocket expenses for care, transportation, and medical treatments.

5.2.7.2 Cognitive testing

As one of the principal symptoms of 'fibrofog' is concentration difficulties, a test of sustained visual attention was carried out during the visit (**Figure 5-2**)[520]. This test was selected as previous studies have found deficits in sustained attention in patients with brain-fog symptoms post-COVID, which phenotypically may resemble the cognitive symptoms seen in fibromyalgia[520].

This was performed during the visit on an Apple iPad with attached keyboard on a Google Chrome browser. The task involved pressing the spacebar when '0' appeared amidst other digits (1-9), masked by a semi-transparent grey checkerboard. Each block lasted 60 seconds, and after a practice block, 9 blocks were performed in total. The hit rate was calculated from correct hits, while false positive rate was calculated from incorrect hits. A composite measure of task accuracy, D', was derived. Reaction time

(RT) for correct hits was measured as the time between the digit appearing on the screen and the spacebar being pressed. RT variability was also assessed.

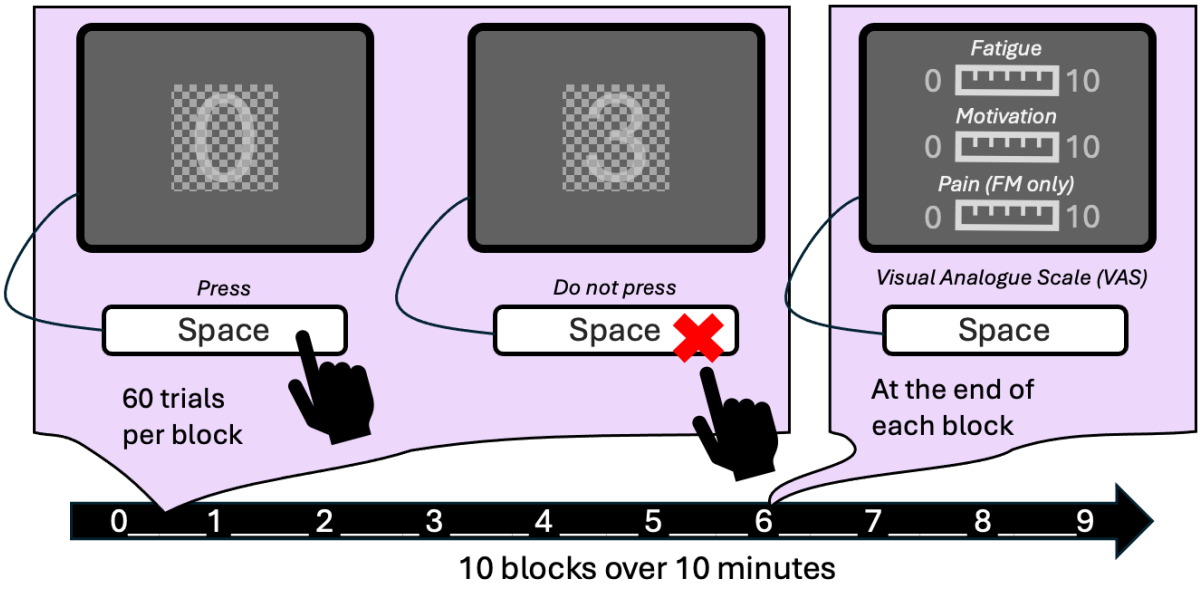


Figure 5-2. Visual sustained attention task.

The task involved pressing the spacebar when '0' appeared amidst other digits (1-9), masked by a semi-transparent grey checkerboard (Zhao 2022)[520]. The hit rate was calculated from correct hits, while false positive rate was calculated from incorrect hits.

5.2.7.3 Actigraphy & sleep diary

Participants were given an actigraphy device (CamNtech MotionWatch 8) to wear on their wrist for 7 days following the baseline and 3-month visit. This device has been used by colleagues in evaluation of *Sleepio* in other patient groups, facilitating comparison of trial results across trials[160]. Alongside this, they were asked to complete the Consensus Sleep Diary each day[73], where they documented sleep times and self-reported sleep quality. Participants were given an envelope and were sent a postage label to return the watch to me after one week.

5.2.7.4 Quantitative sensory testing

Participants underwent an abbreviated quantitative sensory testing (QST) protocol during in-person assessments to evaluate sensory function and detect abnormalities in pain processing, such as central sensitisation, which is often observed in fibromyalgia. The protocol was based on the validated methods developed by Rolke and the German Research Group on Neuropathic Pain[375; 376]. Testing was conducted over a central body site (sternum) and a peripheral site (dorsum of the left hand), using three experimental pain models: mechanical pain threshold (MPT), wind-up ratio (WUR), and pressure pain threshold (PPT). At present, this study does not aim to evaluate QST outcomes; rather, the data were collected for potential future analysis. For detailed descriptions of the QST protocol and methodology, please refer to Appendix D, Section D.6.

5.2.7.5 Magnetic Resonance Imaging (MRI)

A neuroimaging sub-study was nested within the feasibility trial, with eligible participants invited to also undergo a brain MRI at baseline and 12-weeks' follow-up. Neuroimaging data was acquired on a 3T Siemens Prisma MRI scanner at the Oxford Centre for Functional MRI of the Brain (FMRIB) at the John Radcliffe Hospital in Oxford. As outlined above, MRI safety screening was carried out prior to scanning at each visit. Participants were given ear plugs and padding for comfort. For image acquisition, a 32-channel receive-only head coil was used. Participants were instructed to keep their eyes open, and a fixation cross was displayed on the screen. Individual scan

parameters are outlined below. Participants completed whole brain structural, resting state BOLD imaging, and ASL imaging, and H1-MRS of the posterior insula. A fieldmap was also obtained to correct for field inhomogeneities in all echo-planar imaging (EPI) acquisitions. A detailed description of the MRI protocol is provided in Chapter 6 (Section 6.2.2.5), and the appendix (see Appendix D, Section D.7).

5.2.7.6 Other assessments

In addition to the above-described assessments, participants completed other assessments which were outside the scope of the current DPhil project, but form part of future work. These measures included a blood sample, quantitative movement testing, and maladaptive learning tasks (a set of online games evaluate learning and reward sensitivity).

5.2.8 Sample size for feasibility trial

There is little consensus on the appropriate sample size required for feasibility studies to precisely estimate the effect size and variance in order to inform the main trial but recommendations typically range between 24[224] and 50[413] participants.

A systematic review and meta-analysis of 24 randomised controlled trials of CBT-I found an overall moderate effect size (Cohen's d=0.47) on quality of life, with similar effect sizes observed in both face-to-face CBT-I and digital CBT-I subgroups[9]. This effect size is a reasonable expectation in the fibromyalgia population and is a suitable

minimum to seek given that active engagement with CBT-I is required to achieve a meaningful benefit.

Work carried out in fibromyalgia suggests that a 14% improvement in FIQ corresponds to the minimum clinically important effect. When evaluating data collected from 115 fibromyalgia patients in our observational cohort, this corresponds to an improvement of 8.67 points on the FIQR, which corresponds to an effect size of Cohen's d=0.48.

Julious et al. had shown that the gains in precision about the variance obtained for sample sizes greater than 12 in each group are small[224]. Thus, a Cohen's d in the region of 0.5 is anticipated and based on Whitehead's et al. stepped rules of thumb, 15 participants per treatment arm would be required to minimise the sample size required for the main trial detecting a moderate effect size. Therefore, a sample size of 15 participants in each arm (N=30 total) was selected. This sample size should provide sufficient information to inform design of a larger trial seeking to detect a moderate effect (Cohen's d ~ 0.5) of the primary clinical outcome, FIQR[491]. While the risk of imprecision is inherent in small feasibility studies, this sample size provides a balance with practical considerations and provide a robust preliminary estimate of the effect size and variance to inform future sample size calculations.

5.2.9 Feasibility analysis

The primary aim of this project was to evaluate the feasibility of conducting a trial of dCBT-I fibromyalgia patients, including neuroimaging assessments. This will be the

focus of the present chapter, with analysis of baseline characteristics presented in chapter 6.

Both quantitative and qualitative endpoints were examined to determine feasibility[347]. The key objectives were to assess the ability to recruit suitable participants, evaluate the feasibility and appropriateness of data collection methods, measure the acceptability and engagement with dCBT-I, and estimate outcome variability to inform sample size calculations for a future trial. These outcomes were compared against predetermined criteria after 30 participants were randomised to evaluate whether progression to a full trial would be appropriate.

5.2.9.1 Quantitative feasibility endpoints

The quantitative feasibility endpoints of this trial included:

- **Participant recruitment:** The number of potentially eligible participants contacted, the number and proportion who responded to the screening invitation, the number and proportion deemed eligible for participation, and the number and proportion of eligible patients recruited.
- **Recruitment rate:** The rate at which participants were recruited, measured as participants recruited per month.
- **Follow-up rates:** Follow-up rates for both online and in-person assessments at 12 and 24 weeks.
- **Engagement with *Sleepio*:** The proportion of participants who accessed the Sleepio programme and the proportion who completed each session.

- **Outcome variability estimation:** Estimation of the standard deviation and correlations for the primary clinical outcome measure (Fibromyalgia Impact Questionnaire Revised, FIQR) to inform sample size calculation for the full trial.

These data were collected continuously throughout the trial and were assessed after 30 participants were enrolled to evaluate the feasibility of continuing the trial.

5.2.9.1.1 Baseline characteristics

Baseline demographic and clinical characteristics were presented for the feasibility sample, and also stratified by blinded group allocation (A vs B). Continuous variables were described using mean and standard deviation (SD) if normally distributed otherwise median and interquartile range (IQR) were presented. Proportions were provided for binary and categorical variables.

5.2.9.1.2 Primary clinical outcome & sample size calculation for full trial

The SD of the primary clinical outcome, FIQR, was calculated to provide an estimate of variability in the primary outcome. In addition, the correlation in FIQR between baseline and post-treatment follow-up at 3 months was calculated.

Using these values as inputs, I estimated the sample size required to detect a minimum clinically-important difference (MCID) of 14% improvement in FIQ (an older version of the FIQR) at 3 months between the *Sleepio* and standard care control arms[42], corresponding to Cohen's d=0.43. This was used as the FIQ correlates strongly with the FIQR, and provides a useful comparison[43], and the MCID has not been determined for the FIQR.

This sample size calculation was conducted based on using analysis of covariance (ANCOVA) in the full trial[96]. ANCOVA maximises the power to detect a difference in outcome between treatment arms at follow-up by accounting for baseline values of the outcome in each group. The sample size calculation was adjusted by a factor of $1 - r^2$ to account for the correlation between baseline and follow-up values of the outcome. This method assumes that the outcome variable is normally distributed and that the correlations and variances of the FIQR at follow-up do not differ between treatment arms. A range of plausible correlation values and effect sizes were used to assess the robustness of statistical power calculations.

5.2.9.2 Recruitment and retention

- **Response rate**: A response rate of ≥20% of contacted patients to the screening invitation was considered acceptable, based on previous studies of psychological and behavioural therapies in chronic pain populations[297].
- **Consent rate**: A target of ≥70% of eligible patients consenting to participate was set. This was in line with expectations from similar trials and reflected the willingness of the target population to engage with the trial.
- **Recruitment rate**: I sought a minimum rate of ≥4 participants randomised per month, which would be comparable to publicly-funded RCTs[479].
- **Follow-up rate**: A follow-up rate of ≥85% of randomised participants at 3-months was expected, which would demonstrate sufficient participant engagement and minimise attrition bias[285]. This criterion is standard for trials requiring reliable longitudinal data.

5.2.9.2.1 Data completeness

The trial aimed to have <15% missing data for outcome measures at three months post-randomisation[285]. This threshold was chosen to ensure the completeness and reliability of the primary and secondary outcomes, which is critical for the validity of the trial's conclusions. To minimise missing data, automated email reminders were sent to participants for follow-up questionnaires. These were complemented with direct communication from me if they were not completed within one week of the due date. Efforts were also made to accommodate follow-up visits and re-schedule if a participant became unavailable at short notice.

5.2.9.2.2 Engagement with Sleepio

Engagement with *Sleepio*, defined as completing ≥3 out of 6 sessions, was used as a feasibility metric. This threshold was selected as session 3 covered sleep restriction therapy, thought to be the key component of CBT-I[252]. An engagement rate ≥50% was considered acceptable, informed by adherence rates observed in previous Sleepio studies. In studies of primary insomnia, completion rates ranged from 57.6%[139] to 88%[141]. However, in a trial of *Sleepio* for participants with depression, adherence was 53% after 2 sessions[434], with participants benefiting despite lower engagement. Given that comorbid depression is common in fibromyalgia, I deemed a ≥50% engagement rate to be a feasible endpoint for this trial.

5.2.9.3 Qualitative endpoints

A focus group was conducted with participants who completed the 12-week post-treatment assessment to gather qualitative insights regarding the feasibility of the trial. The focus group was held online using Microsoft Teams. A list of topics and questions was prepared in advance (see Appendix D, Section D.8). The session was facilitated with the assistance of two senior researchers in the department (VW & AI), and the Public Engagement team at FMRIB (CP). The session was transcribed using Microsoft Teams' built-in transcription tool, and all transcripts were anonymised for analysis. Data were analysed using a thematic analysis approach to identify patterns and themes within participants' responses[236]. Transcripts were reviewed and coded iteratively, guided by predefined topics and emergent themes (see Appendix D, Section D.8), to explore participants' experiences with *Sleepio* and the trial design.

5.3 Results

5.3.1 Recruitment and retention

In this feasibility trial, 251 patients of OUH and Connect Health were contacted between July and December 2023, of whom 129 (51.4%) responded to the screening invitation, which exceeded the target response rate of 20%. Of these, 73 (62%) were eligible to enrol in the trial of dCBT-I. **Figure 5-3** displays the CONSORT diagram for the flow of subjects through the trial. Reasons for exclusion included a possible sleep disorder (N=13, 23.2%) – most frequently restless legs syndrome –, insufficiently severe symptoms (N=10, 17.9%), or absence of confirmed fibromyalgia diagnosis (N=8, 14%)(**Figure 5-4**). Twenty-five (43.8%) of these ineligible patients were enrolled in the observational study.

Of those eligible, 62 (84.9%) consented to participate in the trial of dCBT-I, with 47 (75.8%) attending or booked for a baseline visit. This exceeded the target of recruiting 70% of eligible patients. Of those randomised, 25 (83.3%) were enrolled in the neuroimaging sub-study. Recruitment to the feasibility trial was completed in under 6 months, with 5.3 patients randomised per month on average, exceeding the target of 4 (**Figure 5-5**). Overall, 12.8% of patients contacted were randomised in the feasibility trial.

Challenges were encountered; in particular, a relatively high proportion of enrolled participants either did not book onto a visit (N=2, 3.2%), did not attend their baseline visit (N=11, 17.7%), or withdrew following their baseline visit prior to randomisation

(N=2, 3.2%). The most common reason for non-attendance or drop-out was illness or a flare of their fibromyalgia symptoms (N=6, 40%). In addition, several participants rescheduled visits due to illness or other reasons prior to attendance at baseline, which posed additional resource issues in the conduct of the trial.

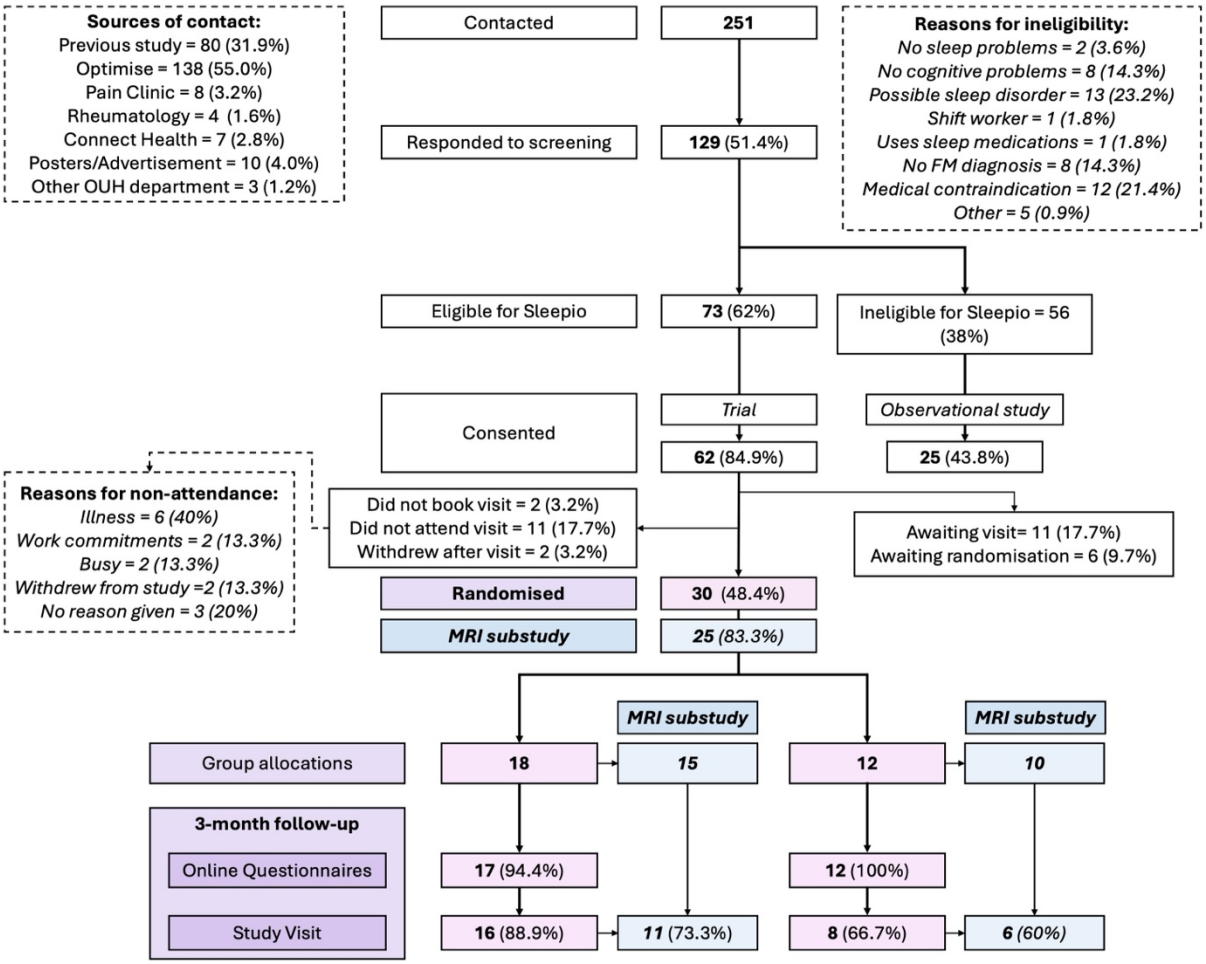


Figure 5-3. CONSORT diagram for flow of participants showing screening, eligibility, and retention rates during the feasibility trial of Sleepio.

Randomisation was stratified by sex and participation in the MRI sub-study. The trial has not been unblinded, and the intervention groups cannot be determined. One participant was lost-to-follow-up from Group A. Participants from a previous observational study of musculoskeletal pain conducted by our research group were contacted and invited to take part in the PainLESS study. CBT-I, cognitive behavioural therapy for insomnia. OUH, Oxford University Hospitals. Optimise is a pain management programme. FM, fibromyalgia. MRI, magnetic resonance imaging.

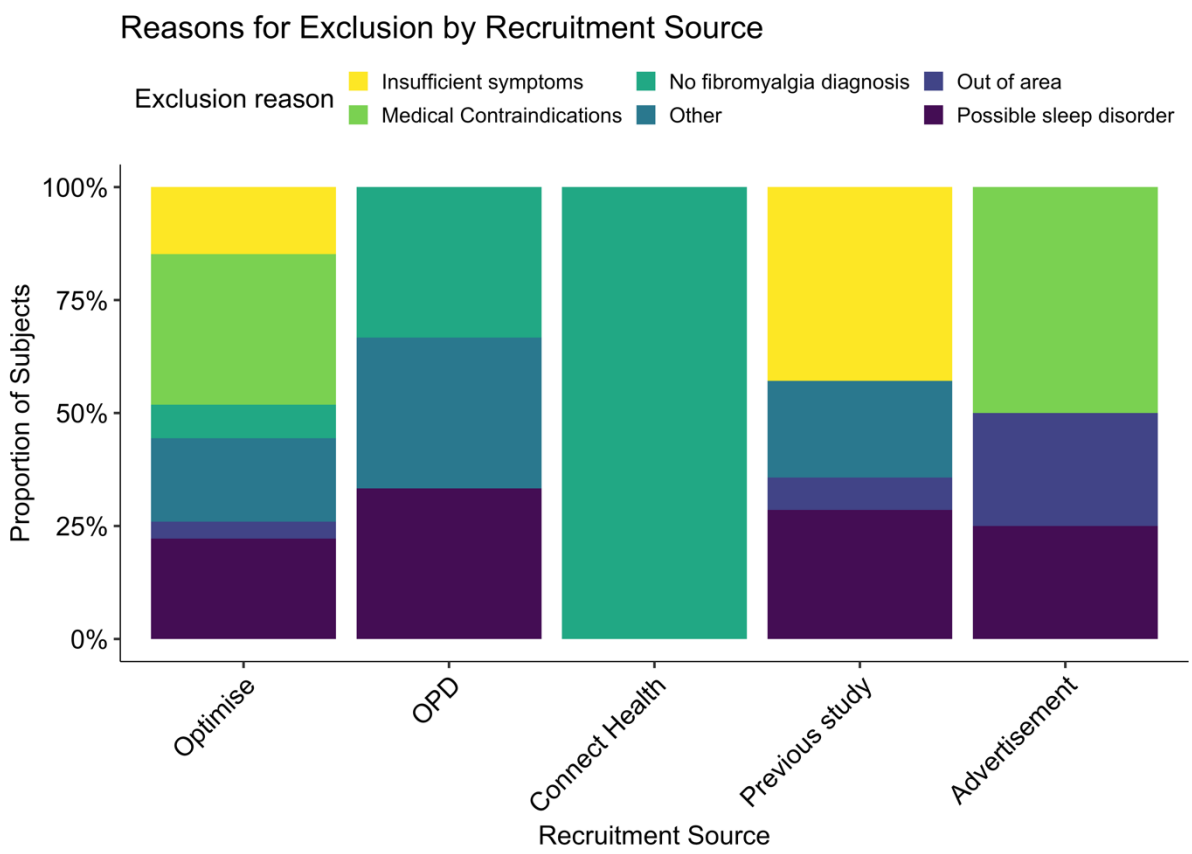


Figure 5-4. Reasons for exclusion of patients who responded to screening questionnaire by recruitment source.

The most frequent reasons for exclusion were history of a possible sleep disorder, insufficiently severe sleep or cognitive symptoms, and medical contraindications to taking part in the trial.

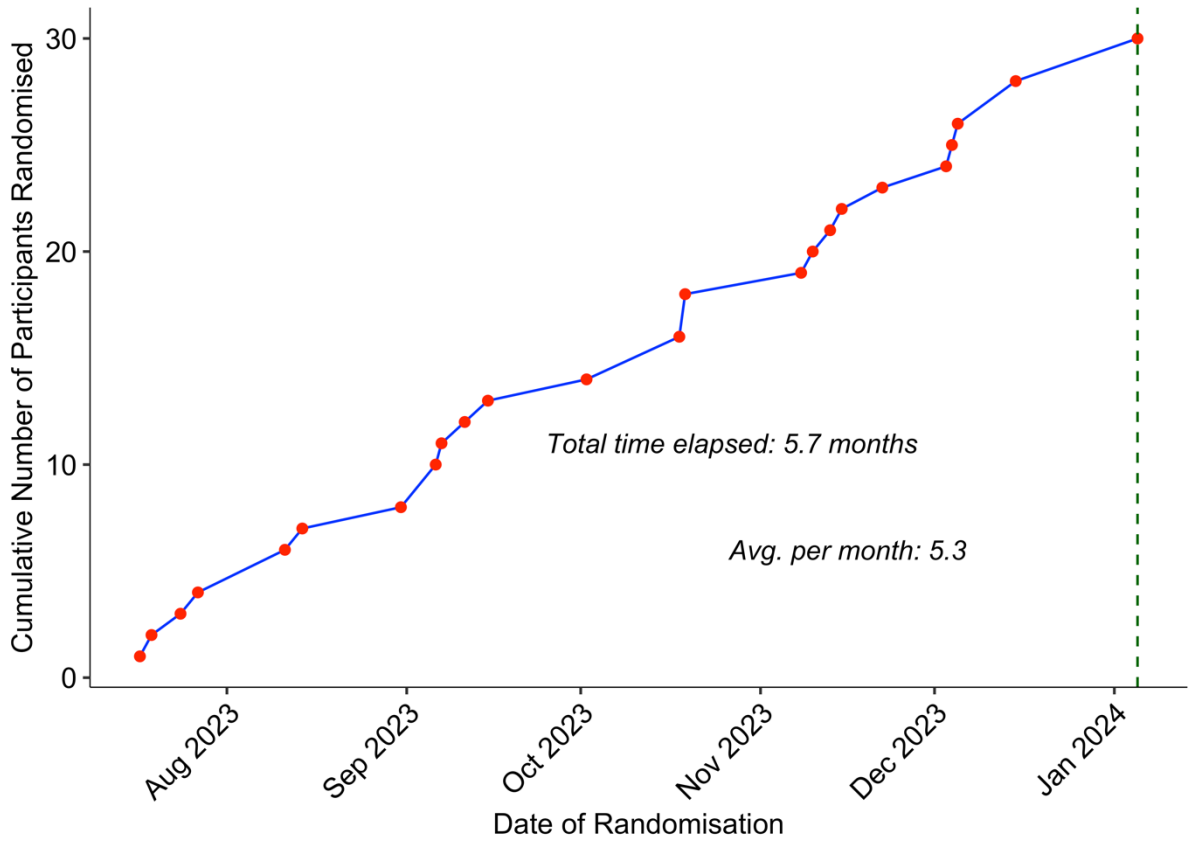


Figure 5-5. Randomisation of participants over time in feasibility trial.

An average of 5.3 participants were randomised per month between July 2023 and January 2024.

5.3.1.1 Recruitment source

The majority of participants were contacted via *Optimise*, the pain management programme in OUH, with 138 (55%) patients contacted from this source. Other sources included patients in already enrolled in a previous observational study in fibromyalgia (N=80, 31.8%), with the remainder being contacted via pain medicine and rheumatology outpatient clinics (N=15, 6%), Connect Health (a community musculoskeletal health service in Oxfordshire (N=7, 3%), or from the advertising materials (N=10, 4%).

Although they made up a small proportion of contacted patients, those who were contacted from outpatient clinics or who heard about the trial through advertisements

showed higher consent and retention rates compared to patients recruited from Optimise or from previous studies, making up 33.3% of randomised participants despite being only 6.8% of contacted patients **(Table 5-4, Figure 5-6).** These patients may be more motivated to participate in research.

Recruitment source	**Contacted, N (%)**	**Randomised, N (%)**	**Randomisation rate, %**
Optimise	138 (55%)	12 (49%)	8.7%
Pain/Rheumatology OPD	15 (6%)	5 (16.7%)	33.3%
Connect Health	7 (2.8%)	1 (3.3%)	14.3%
Previous study	80 (31.9%)	7 (23.3%)	8.8%
Advertisement	10 (4%)	5 (16.7%)	50%
Total	*251 (100%)*	*30 (100%)*	*12.0%*

Table 5-4. Percentage of contacted patients who were randomised, according to recruitment source.

Patients contacted from pain or rheumatology outpatient clinics, Connect Health, and who heard about the trial through advertisements, were most likely to take part and least likely to withdraw from the trial. OPD, pain or rheumatology outpatient clinic. Optimise, pain management programme in Oxford.

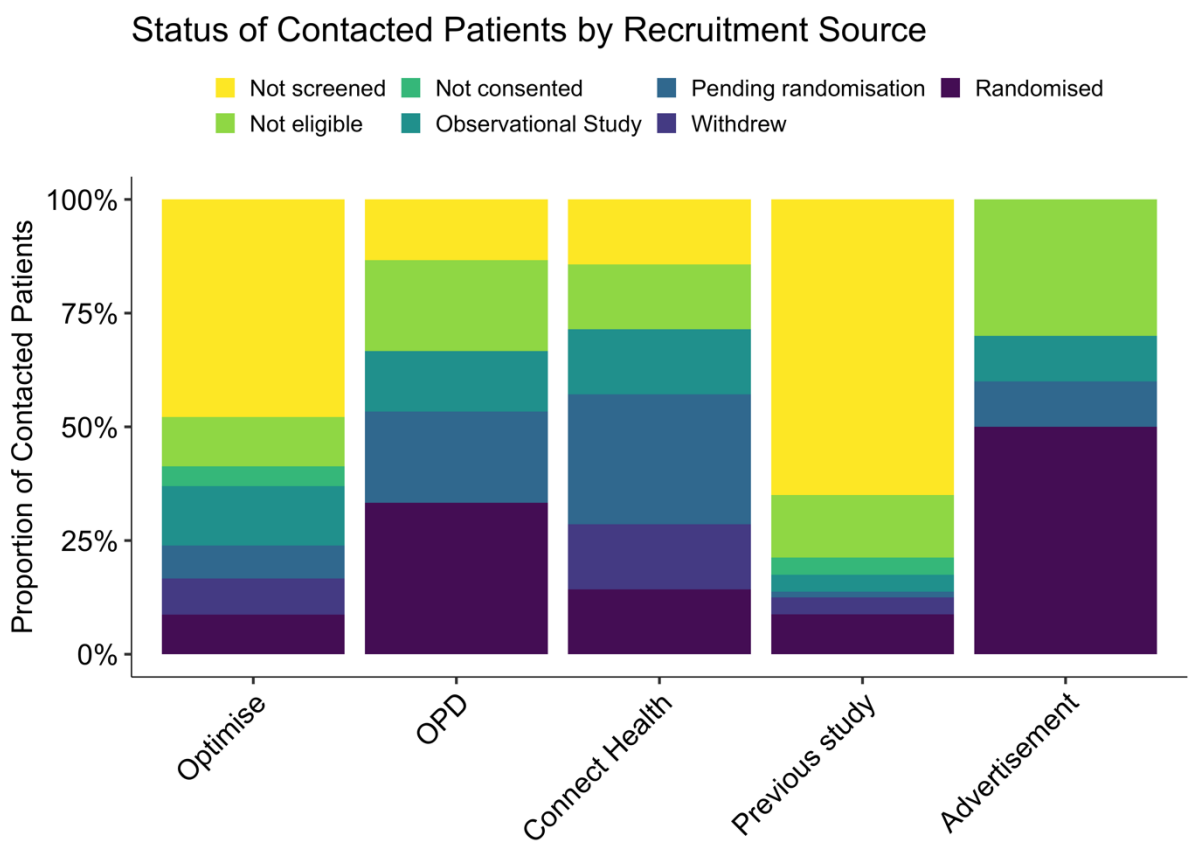


Figure 5-6. Proportion of contacted patients at each recruitment stage stratified by source.

Patients contacted from pain or rheumatology outpatient clinics, Connect Health, and who heard about the trial through advertisements, were most likely to take part and least likely to withdraw from the trial. OPD, pain or rheumatology outpatient clinic.

5.3.1.2 Cancellations

During the feasibility trial, a total of 35 visits were cancelled, comprising 27 baseline visits and 8 follow-up visits (**Table 5-5**). On average, participants cancelled 0.56 visits each, with a median notice period of 0 days (range: 0–6 days). Participants who cancelled visits were more likely to drop out; 15 out of the 35 cancelled visits were associated with participants who later withdrew from the trial.

The most common reasons for cancellation were health-related issues, such as a fibromyalgia symptom flare or other illness (28.6%, 10/35), followed by no-shows without notice (17.1%, 6/35), and cases where no reason was provided (11.4%, 4/35) (Table **5-6**). While some cancelled visits were successfully re-booked, cancellations posed challenges to the trial timeline, particularly among participants who later withdrew. Participants who withdrew prior to randomisation were over twice as likely to cancel visits compared to randomised participants, with a higher proportion of no-shows and cancellations for unknown reasons (**Figure 5-7**).

Status	Participants, N	Baseline or follow-up visits cancelled, N	Cancelled per participant	Baseline cancellations, N	Follow-up cancellations, N
Prior to randomisation	17	4	0.24	4	0
Withdrew before randomisation	15	17	1.13	17	0
Randomised	30	14	0.47	6	8
Total	62	35	0.56	27	8

Table 5-5. Summary of visit cancellations by participant status during the feasibility trial.

Baseline visits were more frequently cancelled compared to follow-up visits.

Reason for cancellation	Number (%)
Health reasons (e.g. illness)	7 (20%)
Fibromyalgia symptoms flare	3 (8.6%)
Personal reasons	3 (8.6%)
Logistical reasons (e.g. transport)	3 (8.6%)
Work commitments	2 (5.7%)
No reason given	4 (11.4%)
No-show	6 (17.1%)
Unknown	7 (20%)
Total	35 (100%)

Table 5-6. Reasons for visit cancellations during the feasibility trial.

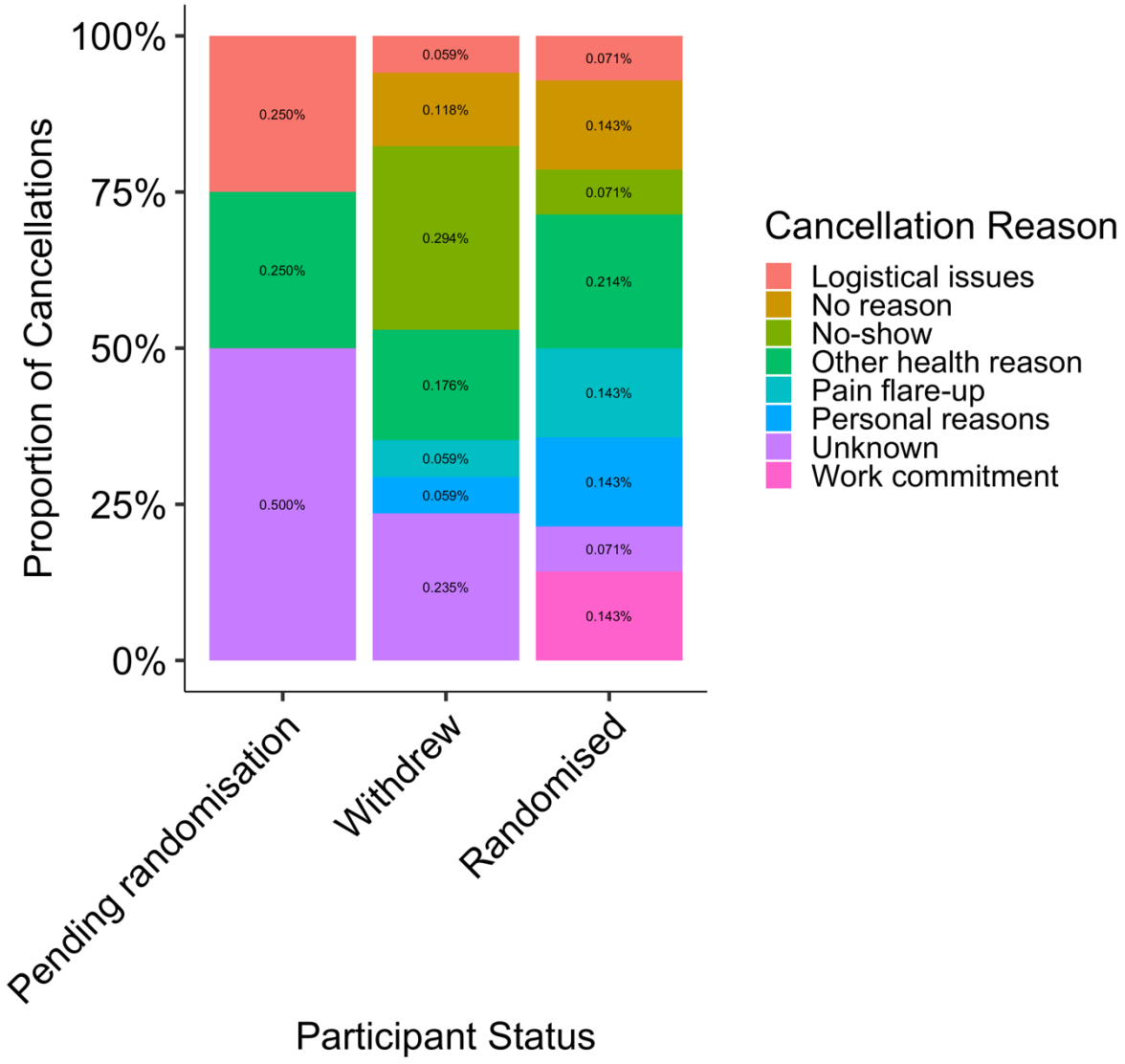


Figure 5-7. Proportions of visit cancellation reasons stratified by participant status

Pending randomisation, Withdrew, and Randomised. Health-related cancellations were frequent across all groups, while no-shows were notably higher among participants who withdrew.

5.3.1.3 Data completeness

Follow-up for the primary endpoint (FIQR) was 96.7% at 3 months, exceeding the target of 85%. Only one participant was lost to follow-up at this time point, with retention dropping slightly to 83.3% by 6 months. Response rates for the primary outcome and key secondary outcomes, including ISI and BC-CCI, were similarly high, with <4% missing at 3 months and <17% missing at 6 months.

In contrast, in-person assessments and neuroimaging follow-up showed greater attrition. One quarter of participants missed the 3-month study visit, and 32% of those with baseline brain MRIs did not complete follow-up scans. Baseline data collection was complete for all trial participants, with the exception of two participants who did not complete the baseline NVT due to headaches.

Despite these challenges, the high retention rate for primary and secondary outcomes supports the feasibility of the trial design. **Table 5-7** and **Figure 5-3** provide a detailed overview of data completeness.

	Completed baseline, N	Completed 3 month follow-up, N	Missing at 3 months, N	% *missing*	Missing at 6 months, N	% *missing*	Missing at 12 months, N	% *missing*
FIQR	30	29	1	*3.33%*	5	*16.67%*	25	*83.33%*
Trial visit	30	24	6	*25.00%*	–	–	–	–
Brain MRI	25	17	9	*32.00%*	–	–	–	–
NVT	28	22	6	*21.40%*	–	–	–	–
Questionnaires								
ISI	30	29	1	*3.33%*	4	*13.33%*	25	*83.33%*
BC-CCI	30	29	1	*3.33%*	5	*16.67%*	25	*83.33%*
SF36-BPS	30	29	1	*3.33%*	5	*16.67%*	25	*83.33%*

Table 5-7. Overview of data completeness for primary (FIQR) and pre-specified secondary clinical outcomes of feasibility trial dCBT-I.

Note that the Trial visit with MRI and NVT were only performed at 3 months' follow-up post-treatment. Trial visit included actigraphy and quantitative sensory testing (QST). FIQR, fibromyalgia impact questionnaire – revised. MRI, magnetic resonance imaging. NVT, numeric vigilance task. ISI, insomnia severity index. BC-CCI, British Columbia cognitive complaints inventory. SF36-BPS, short form 36 bodily pain scale.

5.3.1.4 Primary clinical outcome: FIQR

In the feasibility sample of 30 participants, the mean FIQR at baseline was 57.69 (SD=18.69). At the 3-month post-treatment follow-up, for the overall group, the mean FIQR was 52.24 (SD=19.06). The correlation between baseline and 3-month follow-up FIQR scores was high (*r*=0.86; 95%CI 0.73 to 0.93).

5.3.1.4.1 Sample size calculation

Using the values from Section 5.3.1.4, I estimated the sample size required to detect a minimum clinically-important difference (MCID) of 14% improvement in FIQR at 3 months[42], corresponding to an improvement of 8.08 (Cohen's d=0.43) in this study, equating to a moderate effect size. Assuming a correlation of *r*=0.75 (the lower bound of the 95% CI for correlation), significance level of 0.05 and 80% power, the estimated sample size required to detect a 14% improvement in FIQR amongst participants in the *Sleepio* arm compared to the standard care arm using an ANCOVA is 78 participants (39 per group). This calculation includes an adjustment for a 3.33% loss-to-follow-up rate.

Figure 5-8 & **Figure 5-9** highlight the importance of using ANCOVA to adjust for baseline scores in this study. **Figure 5-8** shows that detecting smaller effect sizes requires larger sample sizes, with 78 participants needed to achieve the MCID at r=0.75. **Figure 5-9** demonstrates that higher baseline-follow-up correlations reduce sample size requirements, emphasising the efficiency of ANCOVA compared to t-tests.

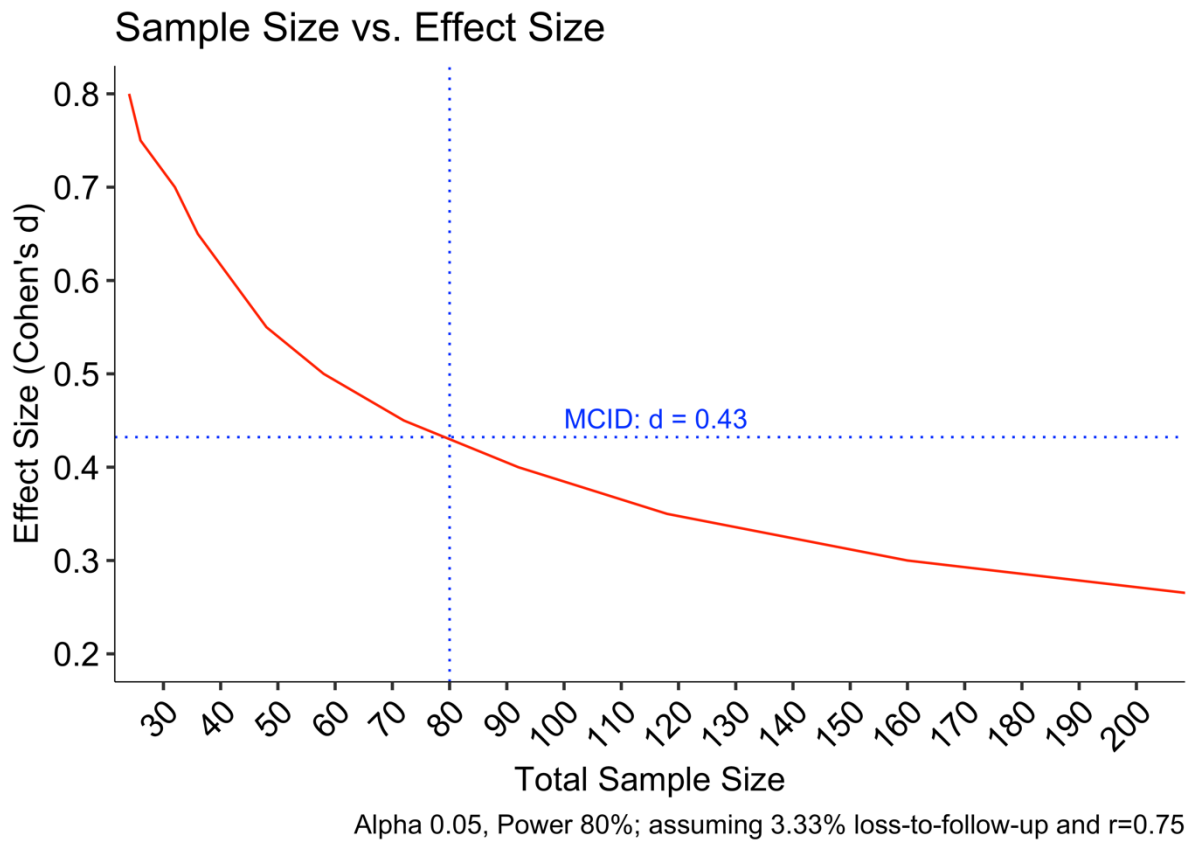


Figure 5-8. Sample size vs. effect size (Cohen's d).

This plot shows the relationship between total sample size and the effect size (Cohen's d) detectable using ANCOVA. This calculation assumes a correlation of 0.75 between baseline and follow-up FIQR values. The dashed blue lines represent the minimum clinically important difference (MCID) of Cohen's d=0.43 and the estimated sample size of 78 participants required to detect this effect at an alpha of 0.05 and power of 0.80, after accounting for a 3.33% loss-to-follow-up rate. Patients randomised on a 1:1 basis.

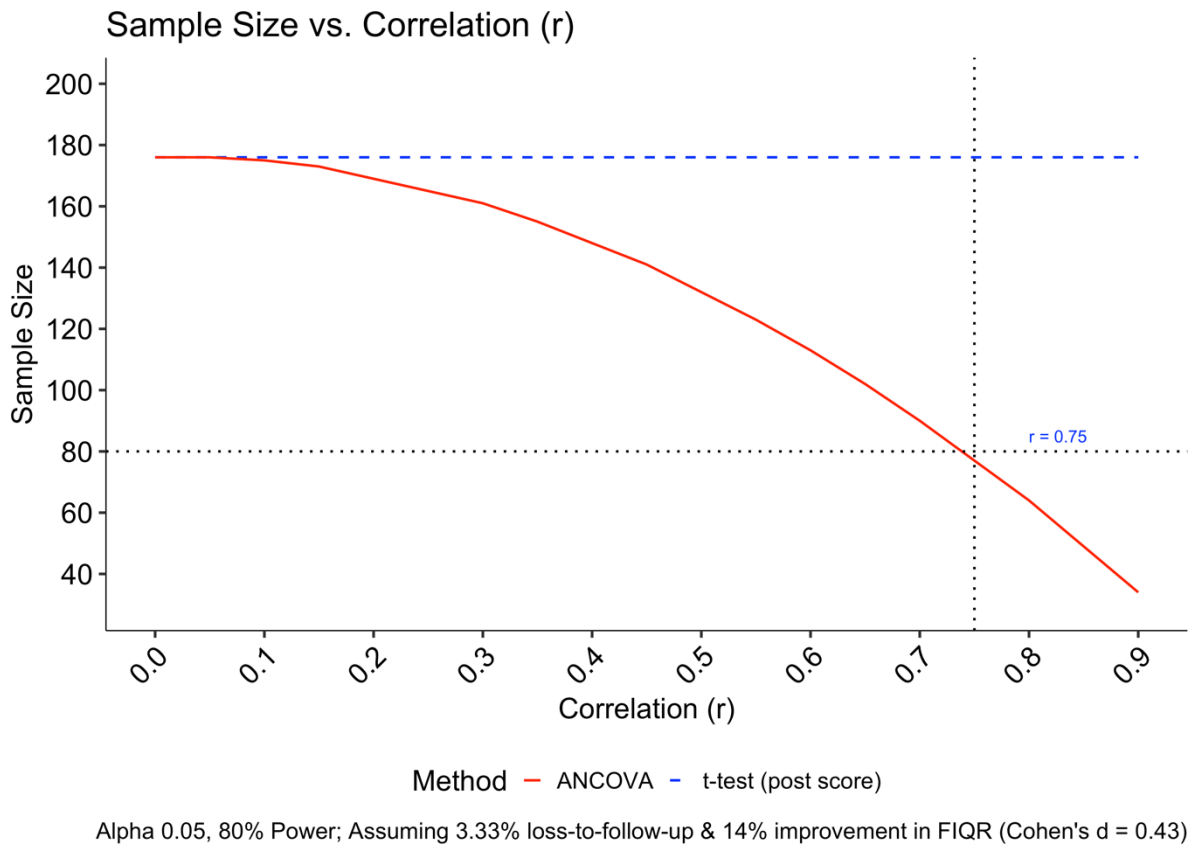


Figure 5-9. Sample size vs. Correlation.

This figure demonstrates how the sample size requirement varies with the correlation (Pearson's r) between baseline and follow-up FIQR values. The red line represents sample sizes adjusted for ANCOVA, which accounts for baseline values. For comparison, the dashed blue line represents the fixed sample size estimated using a t-test (post-treatment score analysis), assuming no correlation between baseline and follow-up. The black dotted line marks the assumed correlation value (r=0.75) used in the sample size estimation outlined, where an estimated sample size of 78 participants (39 per group) would be required to detect the MCID of Cohen's d=0.43 at an alpha of 0.05 and power of 0.80.

5.3.1.5 Engagement with Sleepio

Of 17 participants in the feasibility trial who logged on to *Sleepio* as of January 10th, 2024, 16 (94.1%) started the first session, and 7 (43.8%) completed at least 3 out of the 6 sessions (**Table 5-8**). The same number completed all six sessions in an average of 44.7 (SD 9.8) days. This was slightly below the target adherence rate of 50%.

	Started session, N	**Completed session, N**
Session 1	16	15
Session 2	12	10
Session 3	8	7
Session 4	7	6
Session 5	7	7
Session 6	7	7

Table 5-8. Engagement with Sleepio among feasibility trial participants.

Sleepio consists of six online sessions conducted over 10 weeks. The number of participants who started each session, along with the number who completed each session, is displayed in the table. The program took the 7 participants who have completed all 6 sessions an average of 44.69 days (SD=9.84) to complete. There is uncertainty over the denominator as the number of participants allocated to Sleepio, and how many had completed the treatment period, were unknown as the trial remains blinded

5.3.2 Focus group findings

Eight participants, all female, took part in a focus group conducted via Microsoft Teams. The analysis identified key themes regarding participants' experiences with Sleepio, specifically focusing on their relevance to managing insomnia in the context of other fibromyalgia symptoms such as pain and cognitive dysfunction.

5.3.2.1 Experience with Sleepio

Participants reported mixed experiences with *Sleepio*. Several participants found the programme beneficial for their sleep, and the information on sleep hygiene was generally reported to be useful. However, other participants in the group either found *Sleepio* unhelpful or did not engage with the programme. They highlighted challenges related to usability, cognitive barriers, and motivation in the context of their fibromyalgia. Four themes emerged: 1) Usability and cognitive barriers, 2) Barriers to motivation, 3) Perceived effectiveness, and 4) Sleep and pain interaction.

5.3.2.1.1 Theme 1: Usability and cognitive barriers

Difficulties engaging with *Sleepio* were attributed by some participants to fibromyalgia-related cognitive dysfunction, such as brain-fog and fatigue, as well as issues navigating the programme.

"The first time. I didn't understand what it was telling me to do with the registration and stuff like that. So then I kind of gave up. I'll be honest. I gave up pretty, pretty soon." (Participant 8)

"I was not sleeping well. I mean at all. And I was starting not think straight. I couldn't speak properly. I was like my brain was really almost on 24/7 and I was feeling the impact of that. My cognition was rubbish." (Participant 5)

Despite these barriers, some participants appreciated the programme's overall structure and functionality:

"No, as far as I'm concerned, it worked well. The app was fine. Wearing the watch was fine." (Participant 3)

5.3.2.1.2 Theme 2: Barriers to motivation

Motivation to continue working with *Sleepio* during the treatment period was highlighted as a difficulty with the programme. Initial enthusiasm appeared to wane during over the course of the trial period.

"I need to stick to it to get a result. And it says at the beginning, like, if that's the hardest part, but it will improve and then it really did. But it was really like, Oh my God, I need to leave. I need to go to bed." (Participant 5)

"It got me into a better habit, but it's getting later and later, so I'm getting up later and later, so my day doesn't start till mid-morning." (Participant 6)

5.3.2.2 Theme 3: Perceived effectiveness of CBT-I

Participants expressed mixed experiences with the CBT-I techniques provided by *Sleepio*, particularly regarding sleep restriction and its interaction with fibromyalgia symptoms such as pain. For some participants, *Sleepio* provided benefits by improving sleep quality through sleep restriction and indirectly alleviating certain fibromyalgia symptoms.

“And then with Sleepio they kind of track your sleep and then, you know, it’s all this stuff that it does… I really followed strictly what the app said… I mean my life changed after that." (Participant 5)

"And then with Sleepio they kind of track your sleep and then, you know, it’s all this stuff that it does and like, OK, you can't go to bed at this time. And I was like, I need to go to bed at this time or you need to wake up really early… but I really followed strictly what the app said… I mean my life changed after that." (Participant 5)

However, others found the sleep restriction strategies, in particular, impractical, particularly during pain flare-ups or when symptoms disrupted their routines:

"At one point it was telling me to just have six hours physically in bed. And also that every time I was awake, I had to get out of bed for 15 minutes and I just said, I'm sorry, but I said I can't stick to this." (Participant 3)

Others felt that the programme’s strategies were redundant with their existing sleep hygiene practices:

"I've got to say it did nothing for me. I mean, a lot of it was what I was practising anyway. Going to bed at the same time, dark room, cool room, blah, blah blah. So I was doing that anyway." (Participant 3)

5.3.2.3 Theme 4: Sleep and pain interaction

Pain was a recurring barrier to *Sleepio’s* effectiveness. While some participants noted improvements in sleep, others felt that pain intensity limited the app's utility.

"They didn't take into consideration is my pain when I'm having a bad flare up… I can only focus on the pain and I can't sleep because of the pain, but the app doesn't cover that. If you're in pain." (Participant 2)

“Nothing will make you sleep when you're in pain. You can't get past that.” (Participant 2)

Fibromyalgia-specific symptoms, such as chronic pain, cognitive impairments, and fatigue, posed significant challenges to fully engaging with Sleepio.

"So as soon as I get into bed and that within, even though I've taken painkillers and that within about 20 minutes or so while pain will start and this can go on for hours. So it doesn't matter what the app says or what to follow. I can only focus on the pain and I can't sleep because of the pain, but the app doesn't cover that." (Participant 2)

5.3.2.4 Suggestions for Improvement

Participants offered useful suggestions to improve *Sleepio's* relevance and usability for fibromyalgia patients. In particular, the need for more support in using the programme, and addressing concerns over some aspects – such as beliefs surrounding sleep restriction, which is a somewhat counterintuitive approach to improving sleep – are essential. Furthermore, it was also felt important to manage expectations that Sleepio is unlikely to be a panacea for all symptoms experienced in fibromyalgia.

"I think maybe somebody else coming in kind of going this is what you need to do. Would be helpful." (Participant 8)

"Maybe have a person who can walk you through how to get started and clarify what to do—that would be helpful."(Participant 8)

"I think more information acknowledging that it won't address all the symptoms might have helped." (Participant 6)

5.3.2.5 Reflections on trial design

In addition to specific feedback on Sleepio, participants shared their experiences with the trial design.

Online vs. in-person assessments: While online components were convenient, technical issues and the length of online questionnaires and tasks often caused frustration, particularly in the context of brain-fog. Many suggested shorter, more engaging assessments or hybrid models incorporating in-person support.

Value of peer interaction: Participants appreciated opportunities for sharing experiences, such as the focus group, noting that hearing from others with similar challenges was both validating and motivating.

5.3.2.6 ***Summary***

The focus group revealed both the strengths and limitations of *Sleepio* for fibromyalgia patients. While the structured approach to sleep management was beneficial for some, significant barriers—such as pain, usability issues, and concerns regarding sleep restriction—limited its effectiveness for others. Tailoring *Sleepio* to the specific needs of chronic pain populations, incorporating user feedback, and enhancing flexibility in design could improve its relevance and outcomes.

5.3.3 Future trial

On the basis of these pilot results, funding has been secured to continue the trial to 80 participants, with the sample size powered to detect a moderate effect size on the FIQR, as outlined above. Recruitment is ongoing, with 72 participants enrolled as of September 2024, and the study is projected to complete post-treatment follow-up by Spring 2025.

The trial aims to evaluate the effectiveness of a dCBT-I program, *Sleepio*, compared to sleep hygiene education, in improving fibromyalgia symptom severity as measured by the FIQR over 12 weeks. Secondary objectives include assessing the intervention's effects on cognitive function, sleep quality, and pain outcomes over time, as well as

identifying predictors of response through exploratory neuroimaging analyses. (see Appendix D, Section D.9 for more details.)

Based on the insights gained from the feasibility trial, several changes have been implemented to improve the design and execution of the full trial:

Enhanced recruitment strategies: Recruitment efforts have been intensified through targeting pain and rheumatology clinics at OUH, by working with members of these services with regular reminders that the study is ongoing and seeking participants. In addition, I expanded the advertisement campaign within OUH settings. These strategies aim to address recruitment challenges identified during the feasibility phase, and focusing on the avenues which resulted in the highest proportion of successful randomisations with the lowest withdrawal rates.

Improved retention measures[269]: To reduce the loss to follow-up observed in the trial visits, the frequency of reminders for trial visits has been increased from every second day to daily. These reminders use multiple communication channels (e.g., phone calls, emails, and text messages) to improve participant engagement.

Support for digital intervention: A dedicated research nurse provides structured reminders to participants about logging into Sleepio. However, to maintain the real-world, hands-off nature of the intervention, and to prevent unblinding, I decided against real-time monitoring of participant activity on *Sleepio*. This approach ensures minimal

interference while emphasising the autonomy of participants. However, future research should explore strategies to tailor dCBT-I for chronic pain populations, potentially including adaptations that address specific barriers such as cognitive dysfunction and fluctuating symptom severity.

These modifications aim to improve recruitment, retention, and adherence while preserving the external validity of the intervention.

5.4 Discussion

5.4.1 Summary

In this study, I have successfully evaluated the feasibility of digital cognitive-behavioural therapy for insomnia (dCBT-I) in 30 patients with fibromyalgia. Its nested design within an observational study ensured efficient data utilisation, offering a valuable dataset for future analyses[239].

Recruitment rates were promising, with approximately 1-in-8 contacted patients randomised, similar to, or better than, other studies of CBT-I (**Figure 5-3**). The proportion of trial participants undergoing neuroimaging was high, indicating that neuroimaging could be integrated as a standard component in subsequent trials rather than as an optional sub-study.

Follow-up rates were excellent for the online questionnaires, with 96.7% retention at 3 months and 85% at 6 months (**Table 5-7**), surpassing comparable trials of dCBT-I[141; 253]. While in-person assessments and imaging follow-up rates were comparatively lower, with 80% and 68% retention respectively, they aligned with retention observed in other CBT-I studies in fibromyalgia populations[300]. Engagement with dCBT-I was slightly below expected, with just under half of participants completing the program (**Table 5-8**), lower than the >80% completion rates typically observed in face-to-face CBT-I trials[256; 300]. This underscores the trade-off inherent in digital therapies, where accessibility is improved, but engagement may suffer[516].

Consequently, RCTs evaluating dCBT-I in are essential, as promising results from face-to-face CBT-I in fibromyalgia or digital CBT-I in other conditions cannot be assumed to translate directly. Lower engagement in digital formats may significantly impact efficacy, emphasising the need for condition-specific trials.

Qualitative findings from the focus group indicated that difficulties with sleep restriction therapy (SRT) and the interplay of pain and insomnia in fibromyalgia might have contributed to low engagement, highlighting the need for tailored adaptations of digital CBT-I for chronic pain populations. Similar feedback has been noted for *Sleepio* in other settings, such as in post-stroke patients[417].

5.4.2 Context of findings

5.4.2.1 Previous CBT-I trials in fibromyalgia

Several trials have established the efficacy of face-to-face CBT-I in fibromyalgia, as summarised in Chapter 2 (Section 2.3.5), with effects sustained up to one year[443]. These treatments also demonstrate a beneficial effect on pain, mood, and fatigue, which suggests that interventions targeting sleep may improve quality of life in chronic pain, although this has not previously been studied directly.

In the earliest trial of CBT-I in fibromyalgia, Edinger et al. demonstrated improvements in subjective sleep quality and PSG-assessed total wake time[134]. However, high attrition at 6 months limited conclusions on sustained benefits. Miro et al. explored the effect of CBT-I on executive functions in a small pilot trial, observing significant improvements in attention-alerting linked to enhanced sleep quality[314]. However,

loss to follow-up for cognitive outcomes was high (29.5%), mirroring challenges seen in PainLESS.

The SPIN trial compared CBT-I, CBT for pain (CBT-P), and a usual care group in 113 patients[300]. Both behavioural interventions improved sleep quality compared to the usual care group, but no difference was observed between CBT-I and CBT-P, suggesting the need for further research into the active components of CBT-I in fibromyalgia, which are thought to be SRT and stimulus control[252]. The SPIN trial also included a neuroimaging sub-study, which found an increase in cortical thickness in regions associated with executive functions, suggesting potential mechanisms of improvement[299]. However, high attrition rates (61.5% follow-up) highlight challenges with neuroimaging similar to those in PainLESS.

Lami et al. compared combined CBT-Insomnia/CBT-Pain (CBT-IP) with CBT-P alone and with sleep hygiene, also finding no additional benefit for combined therapy on sleep quality, with follow-up rates of 72% post-treatment and 47% at 3 months[256]. Similarly, Martinez et al. and Sanchez et al. found improvements in sleep quality using face-to-face CBT-I, but high attrition rates (>20%) limit broader generalisability[76; 395].

5.4.2.2 Digital CBT-I in chronic pain and insomnia

In contrast to face-to-face therapies, dCBT-I has not been widely studied in chronic pain conditions such as fibromyalgia. dCBT-I shows comparable benefits in subjective

sleep quality to face-to-face CBT-I, and is promising due to greater accessibility and convenience, particularly in conditions such as fibromyalgia[516].

In a pilot study with *Sleepio* in women with migraines, Crawford et al. reported high engagement (83%), although the lack of a control group limits conclusions[109]. Whibley et al. demonstrated feasibility and acceptability of *Sleepio* in a pilot study in patients with chronic pain due to osteoarthritis, further supporting its potential in chronic pain[488]. Another pilot study of telehealth delivered CBT-I in 10 patients with chronic musculoskeletal pain reported 100% completion and low rates of rescheduling[518]. These pilot studies support the feasibility of alternatives to face-to-face CBT-I in chronic pain. The higher engagement rates seen in these studies may be due to the closer observation of participants, with more regular contact with investigators. This is supported by reviews which show that dCBT-I is more effective with greater clinician contact[516]. However, this produces extra resource burden, and limits the ability to scale up the intervention. Furthermore, it does not reflect current clinical practice in the NHS where ongoing clinical support to accompany dCBT-I is not available.

Despite these pilot studies, RCTs of dCBT-I tools such as *Sleepio* are lacking in chronic pain conditions such as fibromyalgia. In insomnia, however, large trials of *Sleepio* have established its efficacy in improving sleep quality and subjective dyscognition[139; 253]. Espie et al. observed sustained benefits in subjective sleep and quality of life at 6 months, with similar engagement rates to the current PainLESS study (48.4% of participants completed Sleepio). In the DISCO trial, Kyle et al. found that *Sleepio*

improved subjective dyscognition, also measured with the BC-CCI, which was mediated by better subjective sleep quality. However, they found no changes in objective cognitive measures. The DISCO trial used the UK Biobank cognitive battery; these relatively simple tasks may not be sufficiently sensitive to detect subtle changes in cognitive performance[280]. This highlights the need for more sensitive cognitive assessments, which I have tried to address in the PainLESS trial with the number vigilance task (NVT). The NVT has been shown to detect differences in sustained attention between healthy control, post-COVID patients[520], and fibromyalgia (see Chapter 6). Furthermore, both trials did not capture objective sleep measures with actigraphy, or explore underlying mechanisms with neuroimaging.

5.4.2.3 Mechanisms and phenotyping in fibromyalgia and Insomnia

Executive dysfunction and hyperarousal are key features of insomnia and fibromyalgia[26; 88; 471]. Vgontzas et al. identified distinct insomnia phenotypes, with greater executive function impairments in insomnia with *objective* short sleep duration (ISS) compared to insomnia with normal objective sleep duration (INS). In addition, ISS is associated with more pronounced dysfunction of the hypothalamus-pituitary-adrenal (HPA) axis, as demonstrated by higher nighttime cortisol and ACTH levels compared to INS. Furthermore, ISS may be more resistant to CBT-I[32] and may overlap with fibromyalgia, where immune dysregulation and HPA axis abnormalities are implicated[35]. In future work, I plan to examine these phenotypes using actigraphy and neuroimaging, potentially offering new insights into mechanisms underlying treatment response.

5.4.3 Strengths & limitations

5.4.3.1 Strengths

The PainLESS trial is the first, to my knowledge, to study the feasibility of digital CBT-I in fibromyalgia, addressing barriers to face-to-face therapy such as travel difficulties noted in PPIE discussions. This is reinforced by the relatively high number of in-person visits cancelled or rearranged at short notice, pointing to likely difficulties with face-to-face therapy. It also reflects experience in clinical setting, where drop-out rates for pain management programmes in chronic pain are up to 50%, and may be higher in the context of randomisation[51]. In contrast, outcome retention rates for the online questionnaire-based outcomes were high compared to previous CBT-I trials in both chronic pain and insomnia, supporting the trial's pragmatic design.

The trial will address an important research question by examining subjective and objective measures of sleep and cognition, in addition to neuroimaging in a subset, allowing exploration of mechanisms linking sleep, pain, and brain activity. Furthermore, this is the first study will be the first to evaluate ASL and MRS modalities in the setting of CBT-I, potentially offering new insights into the treatments effect on brain function.

5.4.3.2 Limitations

Nevertheless, there are important limitations worth noting. Recruitment was limited to a single-centre cohort in a relatively affluent UK region, with patients recruited mostly from secondary care. This may limit generalisability of study findings.

dCBT-I engagement rates are typically lower than face-to-face interventions, likely affecting efficacy. Engagement rates observed in this feasibility study – albeit with a small sample – suggest engagement is slightly lower compared to trials of *Sleepio* in insomnia. Of note, lack of access to internet or a device to access *Sleepio* was not an issue among patients contacted for the study. Indeed, online treatment options like *Sleepio* were preferred by our PPIE group due to convenience and reduced travel, which can exacerbate fatigue in fibromyalgia. UK data shows high smartphone (96% in highest SES, 84% in lowest SES [Statista 2023]) and internet usage (95% of UK households [OFCOM 2020]) across all socio-economic groups in the UK. Balancing this with barriers to face-to-face CBT-I supports the choice of *Sleepio*.

Focus group feedback highlighted the absence of clinician support, and lack of specific tailoring of Sleepio to chronic pain, as potential barriers. However, the trial was designed to be pragmatic, using an existing clinical tool in a setting which reflects current practice. It was not possible to tailor *Sleepio* for fibromyalgia, and ongoing clinician involvement is not currently available with the programme.

Finally, the study lacked polysomnography (PSG), interim assessments during treatment, and ambulatory assessment of intra- and inter-daily variations in sleep, cognition, and pain. These were omitted as they may pose an additional burden on participants, but would be of value in future studies.

5.4.4 Conclusions and future work

The PainLESS study establishes the feasibility of a trial of dCBT-I in fibromyalgia, demonstrating high retention and recruitment rates. Based on these findings, I have obtained funding to continue the PainLESS study which would be fully powered to detect a MCID in FIQR between the *Sleepio* and standard care arms with a total sample size of 80 patients. By bridging gaps in prior research, PainLESS will contribute significantly to the understanding of how dCBT-I may affect quality of life and a wide range of symptoms in fibromyalgia.

Addressing engagement challenges in dCBT-I and tailoring existing interventions for chronic pain populations should be a topic for future trials. Comparative studies of digital versus face-to-face CBT-I, incorporating active controls, would clarify the active components of therapy. However, it is important first to establish whether current available dCBT-I tools, such as *Sleepio*, work in fibromyalgia. Improved phenotyping using PSG and neuroimaging may enable targeted interventions for fibromyalgia subgroups, such as ISS or INS phenotypes.

6 Chapter Six: Pain-LESS Study: executive function in fibromyalgia

6.1 Introduction

Cognitive dysfunction, often described as "brain-fog," is a frequent complaint among patients with fibromyalgia. These symptoms include difficulties in concentration and memory, severely impacting patients' quality of life. One critical component of attention—sustained attention, or the ability to maintain focus over time—may be impaired in fibromyalgia and could underlie many of these cognitive complaints. Sustained attention deficits are well-documented in conditions such as long COVID and sleep deprivation, both of which share overlapping symptoms with fibromyalgia[131; 132; 226; 519; 520]. However, this domain of cognition has received relatively little attention in fibromyalgia research, despite its clear clinical relevance for everyday tasks such as driving, work, and education.

Sustained attention involves dynamic interactions between bottom-up processes, such as arousal maintenance and reorientation to targets, and top-down mechanisms that control task engagement[89]. These processes collectively address two fundamental challenges of attention: filtering and selecting relevant information from an overwhelming array of sensory inputs, and sustaining focus over prolonged periods. Common measures of sustained attention include *speed* (reaction time, RT), *accuracy* (number of correct responses or errors) and *performance decrement* over time. However, disruptions to this balance between bottom-up and top-down processes can

lead to *state instability*, characterised by fluctuating performance between periods of optimal focus ("in the zone") and attentional lapses ("out of the zone")[142]. This instability may be influenced by internal factors, such as fatigue or motivation, as well as external factors like pain or sleep disturbances[128]. Patients with fibromyalgia often report severe disruptions to sleep, high levels of pain, and fatigue, all of which could contribute to impairments in sustained attention[88]. Yet, the specific contributions of these factors remain poorly understood.

In earlier research using the UK Biobank cohort (Chapter 3), in people with chronic pain, pain intensity, abnormal sleep patterns, and anxiety partially mediated the cross-sectional relationship between nociplastic pain severity and executive function. The SPACE framework, encompassing sleep, pain, affect, cognitive difficulties, and energy, provides a structured approach to examining symptom contributions in fibromyalgia[402]. In Chapter 4, I found that abnormal functional and structural connectivity in the descending pain modulatory system (DPMS), particularly between the periaqueductal grey (PAG) and amygdala, was associated with both nociplastic pain severity and executive dysfunction. These findings suggest that the DPMS, an important pathway for pain modulation, may also play a role in the cognitive impairments observed in fibromyalgia, given that both pain and sleep disruption is prevalent. Emerging evidence also implicates the PAG in disruptions caused by sleep deprivation[449; 486]. Despite these insights, the role of the DPMS in sustained attention deficits has not been directly investigated.

Several key questions remain unanswered: What aspects of sustained attention—such as speed, accuracy, or state instability—are most affected in fibromyalgia compared to healthy controls? Which fibromyalgia symptoms, particularly those related to sleep, pain, affect, cognitive difficulties, and energy (SPACE)[402], are most strongly associated with sustained attention deficits? (3) What are the neural underpinnings of these deficits, and how do they compare to patterns observed in HCs?

6.1.1 Aims & Objectives

To address these gaps, the present study aimed to:

1) Compare sustained attention performance between fibromyalgia patients and healthy controls using the number vigilance task (NVT).
2) Examine how fibromyalgia symptom severity, particularly pain intensity and sleep disturbances, is associated with sustained attention performance.
3) Explore neural correlates of sustained attention deficits in fibromyalgia using resting-state functional connectivity analyses.
4) Derive a neuromarker of sustained attention in fibromyalgia and compare the network pattern to one derived from healthy adults.

I hypothesised that fibromyalgia patients would demonstrate worse accuracy and increased state instability compared to healthy controls, with performance deficits linked to pain and sleep disturbances. Furthermore, I hypothesised that altered PAG-amygdala connectivity would underlie these impairments, reflecting disruptions to DPMS function.

6.2 Methods

6.2.1 Study population

6.2.1.1 PainLESS study

This was a cross-sectional study of participants with fibromyalgia enrolled in the PainLESS study. The PainLESS study is a prospective cohort study of patients with a clinical diagnosis fibromyalgia, with a feasibility RCT of sleep therapy nested within it (see Chapter 5 for a detailed description).

Participants from the trial or observational arms who completed the number vigilance task (NVT) and online questionnaires at the baseline assessment were included in the analysis. For the neuroimaging subgroup analysis, participants who also underwent a brain MRI at baseline were included.

6.2.1.2 Healthy controls

For objective 1, PainLESS participants were compared to healthy controls who completed the NVT. Two-hundred healthy controls were recruited by colleagues from the Department of Experimental Psychology from the University of Oxford, UK and Department of Neurology, Jena University Hospital, Germany. These participants were recruited from Oxford (UK), Jena (Germany), and online through a participant recruitment portal, *Prolific*, as part of a study of brain-fog in long COVID[520]. Those who reported symptoms of long COVID, such as fatigue or brain-fog, or who had a recent COVID infection, were excluded, leaving 178 healthy controls for inclusion. Ethical approval for data collection was granted by the Jena University Hospital ethics

committee (5082-02/17) and South Central—Oxford A Research Ethics Committee (18/SC/0448).

6.2.2 Data preparation

6.2.2.1 Measurements

At the baseline assessment, PainLESS study participants completed a set of online questionnaires including questions about socio-demographics, pain, fibromyalgia symptom severity (FIQR), brain-fog (BC-CCI), sleep (ISI & PSQI), and mood (PHQ-9 & GAD-7). At the study visit, participants were asked about current analgesia use. They completed the NVT and rated their levels of pain, fatigue, and motivation on a VAS before and during the task. A detailed description of the NVT and questionnaires was provided in Chapter 5 (Section 5.2.7.2).

Only limited information on the healthy controls was available at the time of this analysis, with age, NVT performance metrics, and self-rated fatigue and motivation (healthy controls were not asked to rate pain during the task, as this was introduced for the PainLESS study).

6.2.2.2 Number Vigilance Task (NVT)

The NVT is test of visual sustained attention task[520]. Fibromyalgia participants completed the task in person during the baseline assessment (Figure 6-1). The task was completed on an Apple iPad with an attached keyboard and was conducted online via a web browser (*Google Chrome*). Healthy controls completed the task online at home and were also advised to complete it using the Google Chrome browser. All

fibromyalgia participants completed the task in English, while a German language version was provided to German speaking Healthy Controls. The task was implemented with Python v2021.1.2 and hosted on pavlovia.org.

During the task, single digits were presented on the centre of the screen for 50 milliseconds every second. To add difficulty, these digits were obscured with semi-transparent pixels. Participants were asked to press the spacebar when they saw the target digit, "0". They were instructed not to press the spacebar for any other digit (1-9). Each block consisted of 60 trials over 60 seconds, and the probability of the target digit appearing was 25%, and occurred at random.

At the beginning of the task there was a practice phase (Block 0), consisting of 90 trials over 90 seconds, where subjects were provided with feedback (correct vs incorrect response). During the first 12 trials, digits were not obscured by pixels and participants needed to score 100% to proceed. Following successful completion of the practice phase, subjects completed 9 blocks of 60 trials.

At the start of the task, and in between each block, participants were given 15 seconds to rate their current levels of pain ("*How much pain do you have now*?"), fatigue ("*How tired do you feel now*?"), and motivation ("*How motivated do you feel*?") on a VAS.

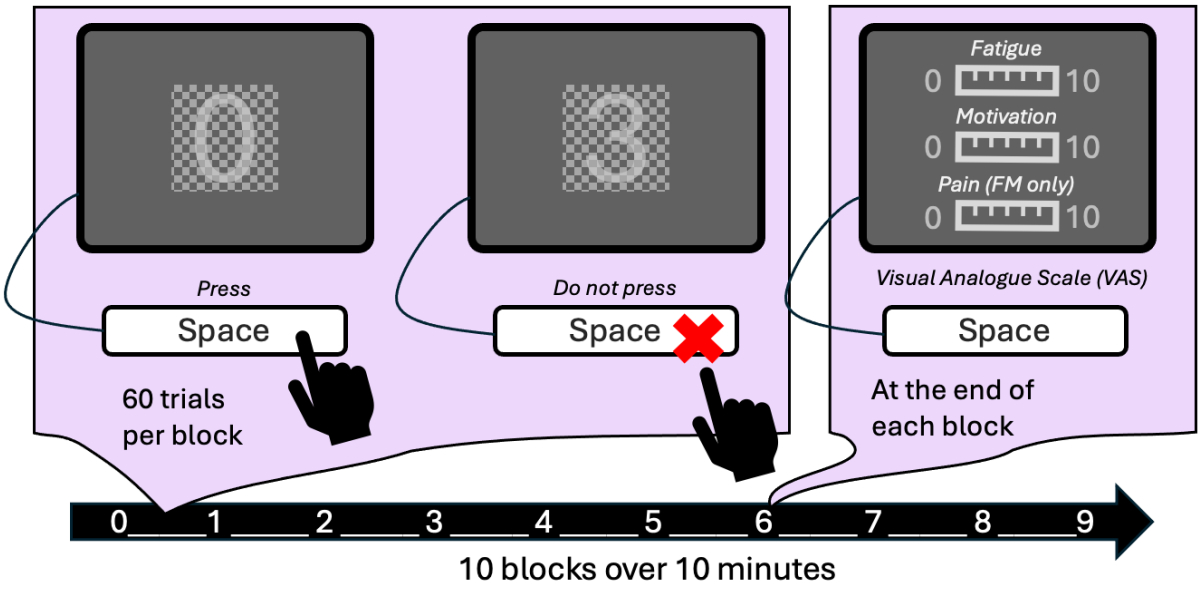


Figure 6-1. Visual sustained attention task.

The task involved pressing the spacebar when '0' appeared amidst other digits (1-9), masked by a semi-transparent grey checkerboard (Zhao 2022)[520]. The hit rate was calculated from correct hits, while false positive rate was calculated from incorrect hits.

6.2.2.2.1 NVT metrics

The following objective performance measures were derived from the NVT:

- **Hit rate (*accuracy*):** the proportion of target digits (0) correctly recognised with a spacebar press, relative to all target digits.
- **False alarm rate (*accuracy*):** the proportion of non-target digits (1-9) incorrectly recognised with a spacebar press.
- **Sensitivity (d', *accuracy*):** This was derived by subtracting the z-score of the false alarm rate from the z-score of the hit rate, with higher values indicating greater sensitivity. To avoid distortions caused by extreme values, the hit and false alarm rates were constrained between 0.00001 and 0.99999 before transformation. This metric was used to assess participants' sensitivity in distinguishing between target ("0") and non-target digits

- **Reaction time (RT, *speed*):** the time between the target digit appearing on the screen and the spacebar being pressed (in seconds).
- **RT variability (*state instability/focus*):** The coefficient of variation for RT was calculated for correct trials by dividing the standard deviation (SD) of reaction times by the mean RT for each participant in each block. This measure provided insight into the consistency of participants' RT across trials, with a higher CV indicating greater variability in reaction speed. This measure provided insight into the consistency of participants' response times across trials, with a higher CV indicating greater variability in reaction speed. RT variability can provide a valuable insight into cognitive fluctuations that accuracy measures may miss[142]. It is sensitive to cognitive changes across psychiatric and neurological disorders, as well as normal aging and development[282]. Increased RT variability is linked to attention and executive function impairments, particularly in conditions like ADHD, where individuals show more inconsistent responses even when accounting for speed[77]. RT variability may capture attentional fluctuations within individuals over time, offering a valuable way to track shifts in task engagement and cognitive performance during sustained attention tasks.

Sensitivity (d') was taken as the primary measures *accuracy* during the task, with hit rate and false alarm rate as secondary outcomes. RT for correct hits was taken as a measure of participants' *speed*. RT variability was taken as a measure of participants' ability to maintain *focus*. The above measures were calculated by taking the mean value across the 60 trials within each block for each participant. In addition, as a

measure of overall task performance, the means were computed from the non-practice blocks across the task.

For baseline pain, fatigue, and motivation, the VAS scores from the first assessment after the practice block were taken. For the mean values across the task, the mean values from after the non-practice blocks were taken.

6.2.2.2.2 Age standardisation

Given the discrepancy in age between the fibromyalgia and healthy control groups, and its important relationship with cognition, age standardisation was performed to control for the influence of age on performance metrics in analyses comparing the two groups[104]. To evaluate potential non-linear associations between age and performance (hit rate, false alarm rate, d', and RT measures), polynomial terms for age were modelled based on the best model fit based on change in AIC and likelihood ratio tests. Based on these analyses, linear terms were fitted for all measures apart from reaction time, for which a cubic term was modelled for age-standardisation. Residuals from these models, which represent the variation in performance after accounting for age, were then adjusted by adding the group means of the raw values. This yielded age-standardised estimates for each metric. For proportion-based variables such as hit rate and false alarm rate, the residuals were normalised to ensure the values remained within a 0 to 1 range.

6.2.2.3 Online questionnaires

Participants with fibromyalgia from the PainLESS study completed the following questionnaires online prior to the baseline study assessment:

- Demographics: Age, sex at birth, self-reported ethnicity, highest level of education attained, current employment status, and duration of fibromyalgia symptoms in years.
- Fibromyalgia symptom severity was assessed using the Fibromyalgia Impact Questionnaire – Revised (FIQR, 0-100; higher scores indicate worse fibromyalgia symptoms).
- Subjective cognitive disturbance was assessed using the British Columbia Cognitive Complaints Inventory (BC-CCI, 0-18; higher scores indicate worse subjective cognitive disturbance).
- Insomnia symptom severity was measured using the Insomnia Severity Index (ISI, 0-28; higher scores indicate worse insomnia symptoms).
- The following self-reported sleep measures were taken from the Pittsburgh Sleep Quality Index (PSQI), total sleep time (TST, hours), time in bed (hours), and sleep efficiency (% of time in bed spent sleeping, derived from 'time in bed'/TST).
- Depressive symptoms were assessed using the Patient Health Questionnaire 9-item (PHQ-9, 0-27; higher scores indicate more severe depressive symptoms).
- Anxiety symptoms were assessed using the Generalised Anxiety Disorder 7-item (GAD-7, 0-21; higher scores indicate worse anxiety symptoms).

6.2.2.4 Analgesia use

During the baseline assessment, fibromyalgia participants were asked by a study investigator (EK or AW) about current use of the following medications commonly used in fibromyalgia: weak opioids (e.g. codeine, tramadol), strong opioids (e.g. oxycodone,

morphine), tricyclic antidepressants (e.g. amitriptyline), and antiepileptics (e.g. gabapentin, pregabalin). Due to the small number reporting strong opioid use, this was combined with weak opioids for analysis.

6.2.2.5 Brain imaging

Fibromyalgia participants in the trial arm were invited to undergo a brain MRI at baseline, including a 12-minute resting-state functional MRI (rs-fMRI) scan. Imaging data underwent extensive pre-processing, including brain extraction, registration to standard space, slice timing correction, noise correction (motion and physiological artefacts), spatial smoothing, and temporal filtering. Full details of pre-processing steps, including motion correction with ICA and fieldmap distortion correction, are provided in **Appendix E** (Section E.1).

6.2.2.5.1 Imaging-derived phenotype

Based on prior findings in UK Biobank (Chapter 4, Section 4.2.4), PAG-amygdala connectivity was selected as an imaging-derived phenotype of interest. Functional connectivity was calculated using the pre-processed rs-fMRI data and region-of-interest masks for the PAG and amygdala. Correlation coefficients were Fisher-Z transformed to standardise values. Detailed methods for this analysis can also be found in **Appendix E** (Section E.1.10).

6.2.3 Statistical analysis

6.2.3.1 Descriptive statistics

Descriptive data of fibromyalgia and healthy controls participants were presented with median and interquartile range (IQR) for skewed continuous variables, means and

standard deviations (SD) for normal continuous variables, and proportions for categorical variables.

6.2.3.2 Objective 1: Compare sustained attention performance between fibromyalgia patients and healthy controls

The unadjusted and age-adjusted mean (SD) values for each NVT metric were presented for the fibromyalgia and healthy control groups. A comparison of average age-adjusted NVT performance and behavioural measures was conducted between the fibromyalgia and healthy controls groups using two-sample t-tests.

6.2.3.2.1 Sustained attention over time

To compare age-standardised performance metrics from the NVT between fibromyalgia and healthy controls, linear mixed-effects models (LMMs) were employed. LMMs is an extension of simple linear regression that assumes observations are independent[414; 457]. These models account for the repeated measures design of the NVT, where participants' performance was repeatedly assessed across multiple blocks. LMMs are mixed as they estimate fixed and random effects. Fixed effects represent population-level average effect across participants and blocks. Random effects model the extent to which these averages vary across participants from the mean fixed effect thus overcoming the lack of independence between observations. The outcome variables included age-standardised sensitivity (d’), age-standardised hit rate (age-standardised TP), false alarm rate (age-standardised FP), age-standardised

RT, age-standardised RT variability, and self-reported VAS measures: fatigue, pain, and motivation.

For each outcome, a LMM was fitted estimating fixed effects for group (fibromyalgia, healthy control) and block, as well as their interaction (group*block), with the hypothesis that patients would fatigue more quickly over time compared to controls. Participant-specific random intercepts were included to account for the repeated measures within individuals. This model allowed for the examination of overall effect of outcome on the fibromyalgia compared to healthy controls, change in outcome as each block was completed, and the joint effect of fibromyalgia and successive completion of blocks. Significance of fixed effects, including the group-by-time interaction, was assessed using the `lme4` and `lmerTest` packages in R[251]. F statistics and associated P-values were reported.

6.2.3.2.2 Speed & focus vs accuracy

I assessed whether participants maintain accuracy by modulating their response speed (speed-accuracy trade-off) or focus (focus-accuracy trade-off). To evaluate speed-accuracy and focus-accuracy trade-offs, I analysed the relationships between mean RT and accuracy measures (hit rates and false alarm rates). Pearson's correlations assessed the overall associations between RT (speed) and RT variability (RTV, focus) with performance metrics, examining whether these trade-offs differed for correct (hit rates) and incorrect responses (false alarm rates).

To explore group differences (fibromyalgia vs. healthy controls), I used linear regression models with interaction terms for group status. Here, as heterogeneity of the effect over

blocks was not of interest, I collapsed all data by subject and had no repeated measures, and thus did not need a LMM. ANOVA was applied to assess the significance of these interactions. All analyses were adjusted for age.

6.2.3.2.2.1 Behavioural measures during NVT

6.2.3.2.2.1.1 Overall group differences

Independent t-tests were used to compare fatigue and motivation levels between fibromyalgia patients and healthy controls during the NVT.

6.2.3.2.2.1.2 Changes over time

LMMs assessed changes in fatigue, motivation, and pain (in fibromyalgia only) over the task duration, including fixed effects for group, time, and group-by-time interactions, with age as a covariate.

6.2.3.2.2.1.3 Effect of fatigue and motivation on performance

Pearson's correlations assessed relationships between fatigue, motivation, and NVT metrics (hit rate, false alarm rate, d', RT, RTV) for the full cohort and by group. To examine whether the relationships differed across the two groups, linear regression models tested group-by-fatigue and group-by-motivation interactions, with ANOVA evaluating interaction significance.

6.2.3.3 Objective 2: Fibromyalgia symptom severity, particularly pain intensity and sleep disturbances, is associated with worse sustained attention performance

This objective examined the relationships between fibromyalgia symptom severity and cognitive performance on the NVT, using speed (RT), focus (RTV), and accuracy (d') as primary outcomes.

6.2.3.3.1 Fibromyalgia symptom severity (FIQR)

The association between total FIQR score and mean NVT performance metrics (RT, RTV, and d') was examined using linear regression models. Two models were fitted: a minimally adjusted model (age and sex) and a fully adjusted model (incorporating additional covariates hypothesised to influence cognitive performance: education (degree, no degree), employment status (employed, not employed), and current use of analgesics (opioids, TCAs, or gabapentinoids)). Likelihood ratio tests (LRT) were used to assess the contribution of FIQR to the models, and changes in R^2 were calculated to determine the variance explained by FIQR.

6.2.3.3.2 Effect of pain, fatigue, and motivation on sustained attention

Baseline levels of pain, fatigue, and motivation were assessed as predictors of mean task performance using the same regression approach as in Section 6.2.3.3.1. LRTs quantified the significance of symptom severity, while changes in R^2 measured explained variance.

6.2.3.3.3 Independent contributions of fatigue, motivation, and pain

Structural equation modelling (SEM) assessed the independent contributions of pain, fatigue, and motivation to sustained attention. Focus (RTV) and accuracy (d') were modelled as outcomes, while RT was excluded due to minimal association with symptoms in prior analyses. Covariances between pain, fatigue, and motivation were explicitly modelled to reflect their interdependence. Given the limited sample size and findings from prior analyses indicating minimal confounding effects, SEM models were adjusted for age only. Model parameters were estimated using bootstrapping with 5,000 iterations to generate robust confidence intervals. Standardised parameter estimates (β) with 95%

confidence intervals were reported to facilitate direct comparison of pathway strengths.

6.2.3.3.4 Independent contributions of pain characteristics

Pain intensity, neuropathic pain (DN4), and widespread pain were analysed as predictors of NVT performance using the methods described in Section 6.2.3.3.3. Independent effects of these pain characteristics were evaluated using SEM, with covariances between predictors modelled to reflect inter-relationships.

6.2.3.3.5 Effect of pain intensity on task performance

LMMs assessed how baseline pain intensity influenced task performance across time blocks, using the same approach described in Section 6.2.3.2.1. Pain intensity was treated as a continuous predictor, with an interaction term (pain × blocks) included to test changes in performance over time. Random intercepts for participants accounted for within-subject variability. To aid visualisation, participants were stratified into high (+1 SD), low (-1 SD), and mean pain groups.

6.2.3.3.6 Brain-fog, affect, and sleep quality

Linear regression and SEM were used to evaluate the effects of brain-fog (BC-CCI), depression (PHQ-9), anxiety (GAD-7), and sleep characteristics (ISI, TST, time in bed, and sleep efficiency) on NVT performance metrics (RT, RTV, d'). Quadratic terms were used for TST and time in bed to account for U-shaped relationships. For SEM, TST and time in bed were dichotomised into normal (7–8 hours) and abnormal (<7 or >8 hours) durations to model non-linear associations[201]. Covariances between predictors were included, and SEM models were adjusted for age.

6.2.3.3.7 FIQR and sustained attention: mediation analysis

This mediation analysis was conducted to examine potential mechanisms underlying the relationship between fibromyalgia symptom severity (FIQR) and task performance, specifically focus (RTV) and accuracy (d'). Given the small sample size and cross-sectional design of this clinical cohort, the analysis aimed to replicate my findings from a larger population-based cohort (UK Biobank, Chapter 3) with greater precision in the measurement of symptom severity and cognitive performance variables.

The mediation models specified two indirect pathways:

- **Pain intensity** (measured using VAS at baseline).
- **Abnormal sleep duration** (binary TST variable: <7 hours or >8 hours, as defined earlier).

These mediators were selected based on their strong associations with task performance in prior analyses and their relevance as potential mechanisms in fibromyalgia-related cognitive impairments. Covariances between pain intensity and TST were modelled to account for their interrelationship.

Direct, indirect, and total effects of FIQR on RTV and d' were estimated. Confidence intervals for all paths were calculated using bootstrapping with 5,000 iterations. Model fit was evaluated using the CFI and TLI, with thresholds of ≥0.90 for acceptable fit. Standardised parameter estimates (β) with bootstrapped 95% confidence intervals were reported for all pathways to allow comparisons.

6.2.3.3.8 Analgesia use and sustained attention

The impact of current analgesic medication use on sustained attention task performance in fibromyalgia patients was assessed. Additionally, the total number of analgesic medications taken (0, 1, or 2+) was assessed to explore the cumulative effects of multiple medications. Independent *t*-tests were conducted to compare NVT performance between medication use groups (e.g., opioids vs no opioids, TCAs vs no TCAs, and gabapentinoids vs no gabapentinoids). For the analysis of total analgesic medications, a one-way ANOVA was performed to compare performance across three groups: 0 medications, 1 medication, and 2+ medications. P-values were reported for each comparison.

6.2.3.4 Objective 3: Explore neural correlates of sustained attention deficits in fibromyalgia using resting-state functional connectivity analyses

The relationship between PAG-amygdala RSFC and NVT performance was assessed using linear regression models incorporating a second-order polynomial term to test for non-linear (U-shaped) associations. Separate models were run for hit rate, false alarm rate, RT, RTV, and sensitivity (d'). Associations between PAG-amygdala RSFC and symptom severity measures (pain, fatigue, motivation, brain-fog, depression, anxiety, and sleep quality) were analysed using the same approach as above.

All models were minimally adjusted for age and sex, with fully adjusted models including education, employment status, and analgesia use. Model significance was determined using likelihood ratio tests to compare models with and without the polynomial term, with changes in R^2 reported.

6.2.3.5 Missing data

For participants with missing covariable data, I conducted a complete case analysis, as the proportion of missing observations for each variable was less than 10%, which is generally acceptable for minimising bias. For participants with missing NVT or MRI data, a complete case analysis was performed as data was assumed to be missing not at random as the reasons for non-completion of the assessments could not be ascertained.

6.2.3.6 Model assumptions

Model diagnostics were performed to assess assumptions of linear regression, including homoscedasticity, normality of residuals, and multicollinearity. Diagnostic plots included residuals vs. fitted values, QQ plots, and histograms of residuals with density curves. Variance inflation factors (VIFs) were calculated to identify multicollinearity. Diagnostics were conducted for both minimally and fully adjusted models.

Data are reported according to the STROBE guidelines[170]. Data preparation and descriptive analyses were performed using the `dplyr`, `tidyr`, `MASS`, `jtools`, `emmeans`, and `stats` packages in R. LRTs were performed using the `lrtest()` function from the `lmtest` package. Variance inflation factor was tested using the `vif()` function from the `car` package. CFA, SEM and mediation analyses were performed using the `cfa()` and `sem()` functions from the `lavaan` package v0.6-18 was used. Data visualisation was carried out using `ggplot2` and `ggpubr`. All

analyses were conducted in R version 4.4.1. Two-sided P-values with significance set at P<0.05 were used for all analyses.

6.2.3.7 Objective 4: Derive a neuromarker of sustained attention in fibromyalgia and compare the network pattern to one derived from healthy adults.

To investigate the relationship between functional connectivity (FC) and cognition in fibromyalgia patients, Connectome-based Predictive Modelling (CPM) was employed. This is a data-driven approach which utilises functional connectivity data to predict individual differences in behaviour. A limitation of the approach is that CPM assumes a linear relationship between FC and behaviour, which may be suboptimal for more complex, non-linear relationships. However, the advantages of CPM over other techniques, such as machine-learning or multivariate methods, is that it is less computationally intensive and simpler to implement, and the predictive networks generated by CPM are easier to interpret compared to weights outputted by multivariate models.

In brief, CPM comprises four steps: 1) feature selection, 2) feature summarisation into a single value, 3) model building and application to behavioural data, and 4) evaluation of prediction significance[157; 409]. Individual FC profiles, derived from resting-state fMRI data, are unique enough to identify individuals across different sessions and conditions. These "functional connectome fingerprints" remain stable across various cognitive tasks and rest states, suggesting a consistent underlying brain architecture that can distinguish one person from another. For example, previous work in healthy

adults has demonstrated that FC profiles, such as in the frontoparietal network, are predictive of cognitive traits like fluid intelligence[157; 409].

6.2.3.7.1 Data collection and pre-processing

FC matrices were derived from the pre-processed resting-state fMRI data in standard space and parcellated into 268 brain regions using the Shen atlas[410]. This atlas was chosen for its coverage of both cortical and subcortical regions, including the cerebellum and brainstem, which are implicated in fibromyalgia. This atlas provides sufficient resolution to capture localised brain activity while minimising noise from minor activity variations across subjects. This atlas has also been used in CPM modelling of sustained attention in healthy subjects, thus permitting model comparison.

6.2.3.7.2 Functional connectivity data and time series analysis

FC time series data for the 268 nodes were extracted using the FSLnets package in Python, generating 35,644 unique edges. Pre-processed FC data were variance-normalised to reduce the influence of extreme values, and reshaped into subject-specific full correlation matrices, followed by r-to-Z transformation. Power spectra for each node were calculated using Fast Fourier Transform (FFT), and the normalised spectra were visualised to assess frequency patterns across the brain. The median spectrum across nodes was also visualised. Time series data for randomly selected nodes and subjects were plotted to inspect temporal patterns.

6.2.3.7.3 Fibromyalgia sustained attention connectome-based predictive modelling (FM-saCPM)

To investigate the relationship between RSFC and sustained attention in fibromyalgia patients, a CPM approach was adapted, termed the fibromyalgia sustained attention CPM (FM-saCPM). The model followed similar procedures to the previously developed sustained attention CPM (saCPM)[380] which here I have applied to a fibromyalgia cohort.

To ensure robustness of the models, k-fold cross-validation was used to divide the dataset into training and test sets, and feature selection was conducted using Pearson correlations between FC edges and d', a measure of sustained attention performance from the NVT. Cross-validation reduces over-fitting as it tests the relationship strength in a novel sample, thus increasing replicability of results[47; 337]. Nevertheless, if there is a large number of features tested, over-fitting is still a risk as a model may be selected which just fits noise[337]. However, limiting the number of features by selecting edges which meet a certain correlation threshold with d' should further reduce the risk of over-fitting. K-fold cross-validation involves partitioning data into *k* folds, where the model is trained on *k*-1 folds and tested on the remaining one. The process is repeated *k* times, and the average accuracy is computed. K-fold cross-validation generates fewer variable estimates of prediction error compared to alternative methods such as leave-one-out cross-validation[242; 503]. In this case, 10 folds were chosen for cross-validation, which provides a reasonable balance between reliability and efficiency[242; 503]. Pearson correlation was used as d' follows a normal distribution. Edges with correlations exceeding an absolute r >|0.3| were grouped into high-attention (positive correlations with d') and low-attention (negative correlations

with d') networks. To prevent data leakage, edges were selected based on their correlation with d' in the training data of each fold, and this was followed by model training and testing. Linear regression models were built using the summed network strengths to predict D'. Separate models were developed for the high-attention, low-attention, and combined networks, and predictions were generated for each test subject.

To assess model stability, 1,000 iterations of the k-fold cross-validation were performed, generating distributions of correlation values and regression coefficients. The mean and SD of the regression coefficients were calculated to quantify the model's consistency across iterations.

To evaluate statistical significance, permutation testing was conducted on the full dataset by shuffling d' scores across participants and recalculating the correlations 10,000 times. This generated a null distribution of correlation values. The observed correlation values were then compared against this null distribution to compute non-parametric p-values, allowing for an estimation of the statistical significance of the model's predictions.

To visualise the networks most strongly associated with d', the aggregated masks for the positive and negative models were plotted on a brain surface using predefined coordinates in MNI space from the Shen-268 atlas, with the edges consistently present in 95% of k-fold iterations presented. Separate plots were generated for high-attention and low-attention models. Edges were also visualised grouped by canonical resting

state network (medial frontal, frontoparietal, default mode, subcortical-cerebellum, motor, visual I, visual II, and visual association[421]).

The FM-saCPM model was also applied to predict other outcomes, including subjective cognitive disturbance (BC-CCI scores) and pain, using the same procedures.

6.2.3.7.4 Application of the sustained attention connectome predictive model (saCPM)

The sustained attention CPM (saCPM) model, described by Rosenberg et al.[380] to predict attention-related behaviour, was applied to functional connectivity and behavioural data from this study. The saCPM model has been demonstrated to predict attention across a range of conditions both within and across individuals and can predict ADHD symptom severity[379]. In contrast to the FM-saCPM model described earlier, the saCPM model was trained on data from healthy volunteers. In addition the sustained attention task used (the gradual onset continuous performance task, gradCPT[142]) differed from the NVT in two important respects: instead of numbers, the stimuli were landscapes; and subjects were required to press the button and to omit this button-press when they saw the target stimulus.

In this study, the saCPM was applied to rs-fMRI data from fibromyalgia patients to predict sustained attention (d') and subjective cognitive disturbance (BC-CCI scores). Spearman correlations were calculated between predicted and observed scores. To assess stability, 1,000 iterations of 10-fold cross-validation were conducted, and statistical significance was evaluated using permutation testing with 1,000 shuffles of the behavioural data, generating a null distribution of correlations for comparison.

6.2.3.7.5 Overlap between saCPM and FM-saCPM models

To better understand the shared neural basis for sustained attention in fibromyalgia and healthy subjects, the overlap between the FM-saCPM and saCPM models was assessed by identifying shared high- and low-attention network edges. Network visualisations highlighted overlapping edges in each network to explore similarities and differences in sustained attention-related FC patterns between fibromyalgia patients and healthy subjects. Permutation testing was used to evaluate the statistical significance of the overlap, with 1,000 random permutations generating a null distribution of overlaps.

6.3 Results

6.3.1 Study participants

Of the 107 fibromyalgia participants enrolled in the PainLESS study as of 11th September 2024, 72 (67.3%) completed the number vigilance task (NVT), primarily from the trial arm (N=66, 92.7%). Healthy control data from 178 participants were provided by colleagues in Oxford and Jena (**Figure 6-2**).

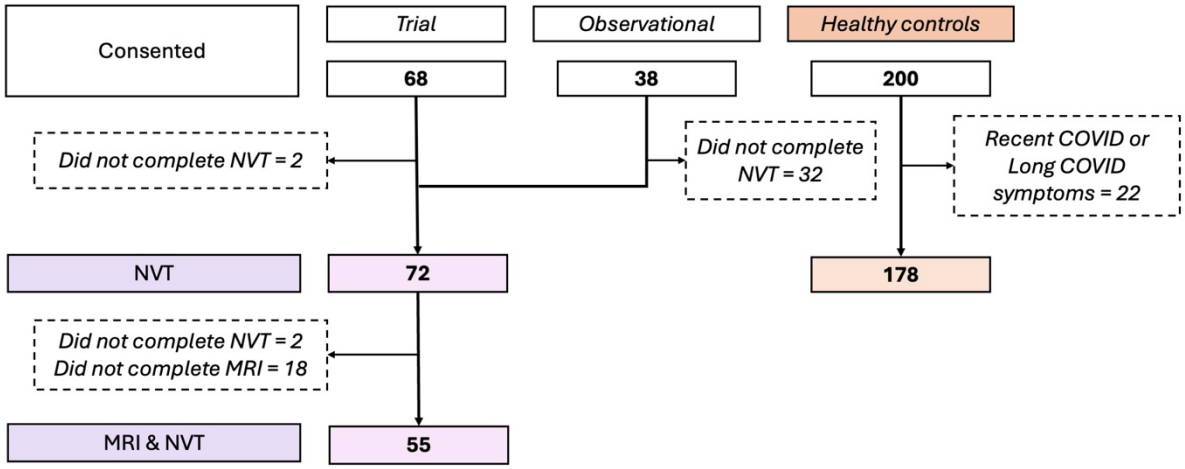


Figure 6-2. Study flow diagram for participants in cross-sectional analyses of relationship between fibromyalgia and sustained attention.

NVT, number vigilance task. MRI, magnetic resonance imaging. Note that healthy control data came from data collected by colleagues at the Department of Experimental Psychology, Oxford, UK, and Jena University Hospital, Germany.

6.3.2 Baseline characteristics

Baseline characteristics for the 72 participants with fibromyalgia are presented in **Table 6-1.** The median age was 49.7 (range 20.7-73.1) years, 91.7% (N=66) of participants were female, and 90.3% (N=65) reported white ethnicity. Thirty (41.7%) participants had a university degree, and just over half (N=42, 56.9%) were in full or part-time

employment, with almost one quarter (N=17, 23.6%) reporting they were unable to work due to illness. The median symptom duration was 7 (range 0.5-57) years, and roughly half of participants report using at least one analgesia medication (N=37, 51.4%), including opioids (N=28, 38.9%), TCAs (N=17, 23.6%) or gabapentinoids (N=9, 12.5%). Participants also reported high levels of cognitive complaints, sleep disturbance, and depressive and anxiety symptoms. Baseline characteristics of excluded participants were broadly similar, apart from slightly higher FIQR scores (64.7 vs 55.6; P=0.067) (Supplementary Table E-1).

Healthy controls (N=178) had a mean age of 32.2 years (SD 13.2), with a median age of 27 (range 18-65). Further baseline characteristics for the control group were unavailable.

Age-related associations with NVT performance, described in Appendix E (Section E.3), showed linear associations for most metrics, except RT, which followed a cubic relationship.

Variable	Total
	(N=72)
Age, years	
Median [Min, Max]	49.7 [20.7, 73.1]
Sex, N (%)	
Female	66 (91.7%)
Male	5 (6.9%)
Prefer not to say	1 (1.4%)
White ethnicity, N (%)	65 (90.3%)
University degree, N (%)	30 (41.7%)
Employment status	
Full time employment	26 (36.1%)
Part time employment	15 (20.8%)
Full time education	1 (1.4%)
Retired	8 (11.1%)
Unable to work due to illness	17 (23.6%)
Unemployed	2 (2.8%)
Prefer not to answer	3 (4.2%)
Symptom duration, years	
Median [Min, Max]	7.00 [0.500, 57.0]
Opioid use	28 (38.9%)
TCA use	17 (23.6%)
Gabapentinoid use	9 (12.5%)
Number of current analgesics	
0	35 (48.6%)
1	20 (27.8%)
2	17 (23.6%)
Fibromyalgia Index (0-31)	
Median [Min, Max]	20.5 [0, 28.0]
Widespread Pain Index (0-19)	
Median [Min, Max]	12.0 [0, 19.0]
Symptom Severity Score (0-12)	
Median [Min, Max]	9.00 [0, 12.0]
Fibromyalgia Impact Questionnaire Revised (0-100)	
Mean (SD)	55.6 (17.3)
PainDETECT (0-38)	
Mean (SD)	18.4 (6.82)
British Columbia Cognitive Complaints Inventory (0-18)	
Mean (SD)	11.3 (3.56)
Patient Health Questionnaire 9-item (0-27)	
Mean (SD)	12.2 (5.47)
Generalised Anxiety Disorder 7-item (0-21)	

Variable	Total
Mean (SD)	6.74 (5.34)
Insomnia Severity Index (0-28)	
Mean (SD)	16.8 (5.74)
Total Sleep Time, hours	
Median [Min, Max]	6.00 [3.00, 10.0]
Time in Bed, hours	
Median [Min, Max]	8.58 [5.00, 12.0]
Sleep efficiency, %	
Mean (SD)	66.6 (15.9)

Table 6-1. Baseline characteristics of participants included in the analysis of sustained attention in fibromyalgia.

Fibromyalgia symptom severity was assessed using the Fibromyalgia Impact Questionnaire Revised (FIQR), with higher scores indicating more severe symptoms. The Fibromyalgia Index (FMI) is the sum of the Widespread Pain Index (WPI) and Symptom Severity Scale (SSS). Depression was measured using the Patient Health Questionnaire 9-item (PHQ-9), with higher scores indicating more severe depression symptoms. Anxiety was assessed using the Generalised Anxiety Disorder 7-item scale (GAD-7), with higher scores indicating more severe anxiety symptoms. Brain-fog was measured using the British Columbia Cognitive Complaints Inventory (BC-CCI), where higher scores reflect greater cognitive difficulties. Neuropathic pain symptoms were assessed using PainDETECT, with higher scores indicating more severe neuropathic symptoms. Insomnia was evaluated using the Insomnia Severity Index (ISI), with higher scores representing greater severity. Total sleep time, time in bed, and sleep efficiency were self-reported and taken from the Pittsburgh Sleep Quality Inventory (PSQI). SD=standard deviation.

6.3.3 Objective 1: Compare sustained attention performance between fibromyalgia patients and healthy controls

Participants with fibromyalgia showed worse overall task performance compared to healthy controls, including worse accuracy and focus. Adjustment for age attenuated these differences but did not eliminate them. Detailed results are provided in Appendix E (Section E.4.1).

6.3.3.1 Objective 1: Fibromyalgia associated with impaired accuracy and focus without accelerated decline

During the task, accuracy deteriorated for both groups, as hit rate declined and false alarm rate increased, in keeping with a large decrease in sustained attention over time (**Figure 6-3A&B**, Hit rate: F=213.63, P<0.001. False alarm rate: F=236.54, P<0.001). There was no change in d' or RT during the task (**Figure 6-3C&D**, D': F=1.32, P=0.251. RT: F=0.64, P=0.423). As described above, compared to healthy controls, the fibromyalgia group displayed significantly worse age-adjusted hit rate (**Figure 6-3A,** F=7.24, P=0.008), false alarm rate (**Figure 6-3B,** F=12.44, P<0.001) and RT variability (**Figure 6-3E,** F=8.68, P<0.001), with moderate-to-large effect sizes observed. However, there was no difference in d' (**Figure 6-3C**, F=2.6, P=0.108) or RT (**Figure 6-3D,** F=0, P=0.974). There was a significant group-by-time interaction for false alarm rate (**Figure 6-3B,** F=42.35, P<0.001), with a large effect size, with the fibromyalgia group starting off worse by converging with the healthy control group over time. These findings suggest poorer overall performance in fibromyalgia patients but no evidence of a greater rate of deterioration compared to healthy controls.

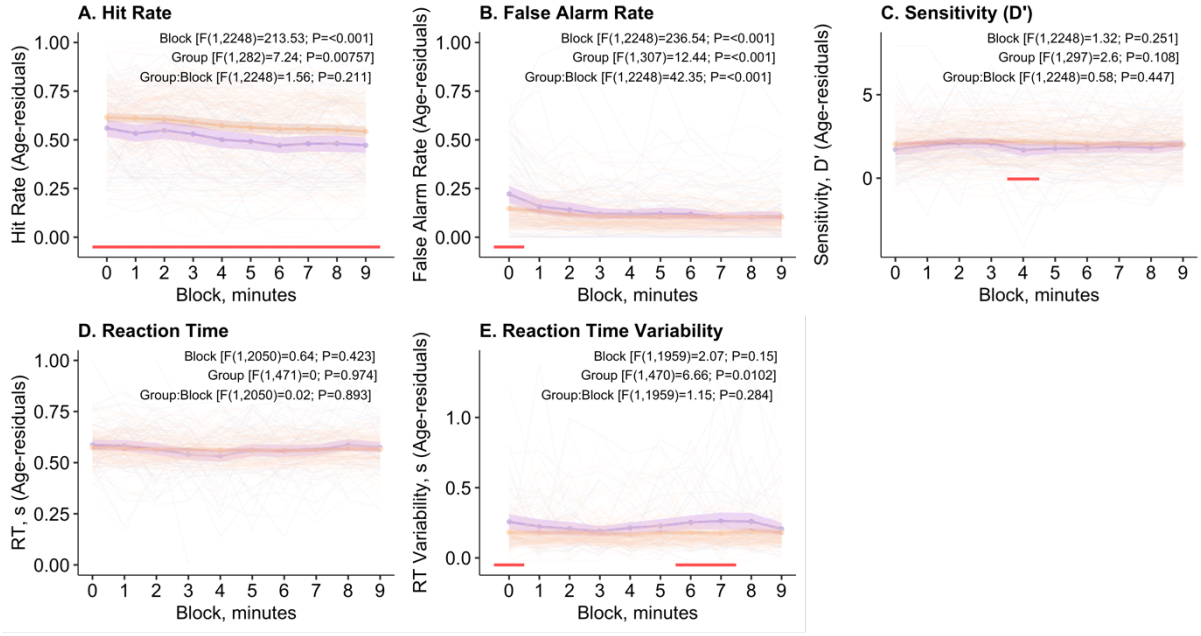


Figure 6-3. Fibromyalgia impairs accuracy and focus without accelerating decline.

Results of linear mixed models annotated with main group and group-by-time interactions reported. Fibromyalgia (FM, purple) patients (N=72) show significantly worse hit rate (A) and false alarm rate (B), and reaction time variability (E) compared to Healthy Controls (HC, orange; N=178), with no significant difference in sensitivity (C) or reaction time (D). However, fibromyalgia patients do not exhibit a faster rate of deterioration in performance (Group:Block interaction). Red lines indicate blocks where there was a significant difference in performance on a post-hoc t-test. Individual trajectories and mean values with 95%CI are displayed. All parameters are age standardised.

6.3.3.2 Objective 1: Speed-accuracy trade-off more pronounced in fibromyalgia

Slower RT were associated with lower hit rates (accuracy) in both fibromyalgia and healthy controls (**Figure 6-4A**, r=-0.42, p<0.001 for fibromyalgia; r=-0.54, p<0.001 for healthy controls), with no significant group interaction (F=2.19, p=0.14). However, faster RTs were linked to higher false alarm rates (errors) in fibromyalgia (**Figure 6-4D**, r=-0.34, p=0.0048), but not in controls (r=-0.07, p=0.35), with a significant interaction (F=6.5, p=0.011) and intersecting slopes suggesting fibromyalgia patients exhibit a stronger speed-accuracy trade-off. No significant interaction was observed for RT for incorrect responses (**Figure 6-4B&E).**

Greater RT variability (worse focus) was associated with worse accuracy and more errors in both groups (**Figure 6-4C**, Hit rate: r=-0.39, p=0.0011 for fibromyalgia; r=-0.39, p<0.001 for controls), with significant interactions (**Figure 6-4C&F,** Hit rate: F=9.37, p=0.0025; False alarm rate: F=15.79, p<0.001). However, the shallower slope in the fibromyalgia groups suggests this observation may be due to a greater spread of RT variability values in these participants.

These findings highlight a more pronounced speed-accuracy trade-off in fibromyalgia, with greater difficulty maintaining accuracy at higher speeds, particularly in reducing errors.

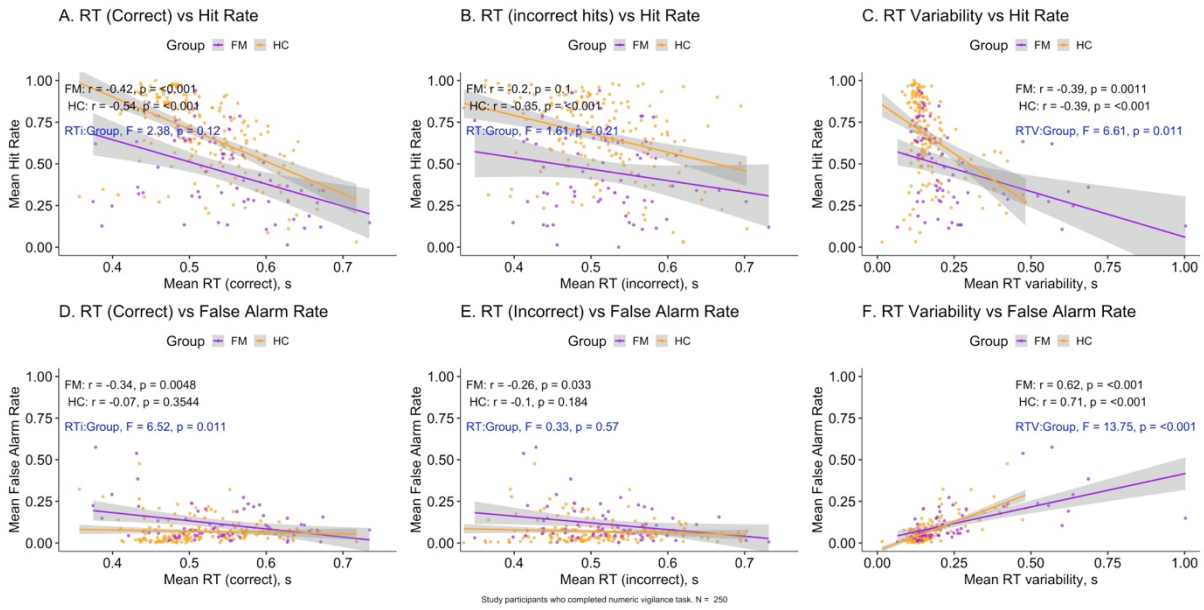


Figure 6-4. Speed-accuracy trade-off more pronounced in fibromyalgia

Fibromyalgia (FM) patients and healthy controls (HCs) demonstrate distinct patterns of associations between reaction time (RT) measures and performance on the number vigilance task (NVT). Both groups exhibit significant negative correlations between faster RT for both correct and incorrect hits and better accuracy (higher hit rates, A&B), with no significant group interaction (F=2.19, p=0.14). In both groups, better focus (lower RT variability) was associated with better accuracy (C).

In contrast, while faster RT was modestly associated with higher false alarm rates in fibromyalgia patients, this relationship was weaker and non-significant in Healthy Controls (D&E). The significant interaction term (F=6.5, p=0.011) suggests differences in how response speed influences false alarms between the groups.

Meanwhile, in both groups, better focus (RT variability) was associated with lower false alarm rates (F). The significant interaction (F=15.79, p<0.001) indicates that fibromyalgia patients may experience greater focus-driven errors.

Slopes with 95% confidence intervals are shown for each group. Pearson's correlation coefficients (r) and p-values are annotated for each group, alongside interaction effects from ANOVA. FM, fibromyalgia. HC, healthy control. RT, reaction time.

6.3.3.3 Objective 1: Fibromyalgia patients report higher fatigue and lower motivation

Patients with fibromyalgia reported higher fatigue and lower motivation levels compared to healthy controls during the task. Further details are provided in Appendix E (Section E.5).

6.3.3.4 Objective 1: Fatigue increases similarly, motivation declines more slowly in fibromyalgia

Self-reported fatigue, motivation, and pain levels increased throughout the task, with large effect sizes observed (**Figure 6-5**, $P<0.001$ for all). While fibromyalgia patients had significantly higher fatigue (**Figure 6-5A**, $F=7.44$, $P=0.0068$) and lower motivation (**Figure 6-5B**, $F=28.08$, $P<0.001$), the rate of fatigue increase over time was similar across groups ($F=0.67$, $P=0.414$). Motivation, however, showed a significant group-by-time interaction ($F=19.92$, $P<0.001$), with healthy controls starting more motivated but declining faster than fibromyalgia patients. In the fibromyalgia group, pain steadily increased during the task (**Figure 6-5C**, $F=158.64$, $P<0.001$). Pain levels were not assessed in healthy controls.

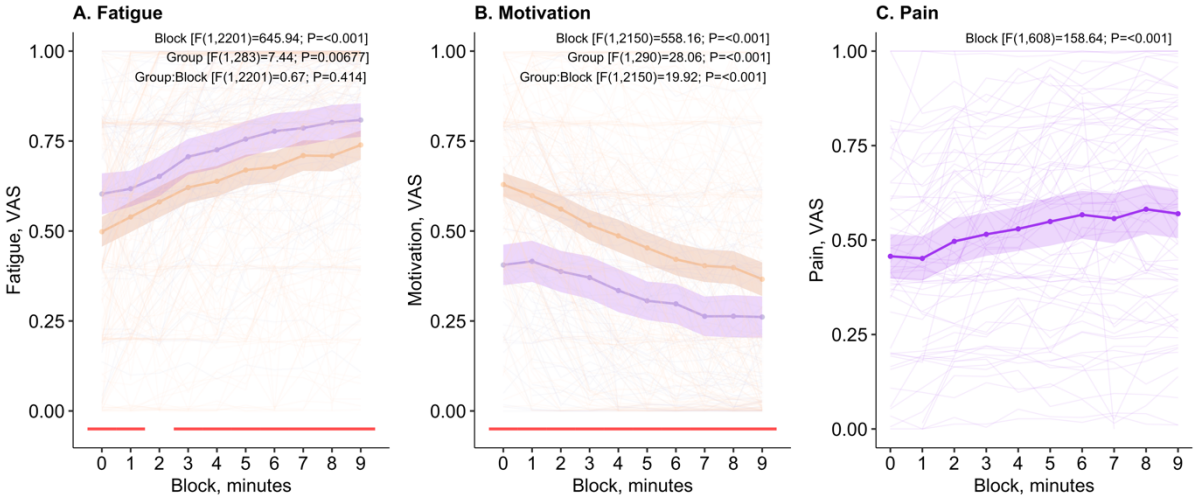


Figure 6-5. Fatigue increases similarly, motivation declines more slowly in fibromyalgia.

During the task, fibromyalgia patients (purple, N=72) report higher fatigue (A) and lower motivation (B) compared to healthy controls (orange, N=178). In the fibromyalgia group, pain increases during the task (C). Results of linear mixed models annotated with main group and group-by-time interactions reported. Red lines indicate blocks where there was a significant difference in performance on a post-hoc t-test. Individual trajectories and mean values with 95%CI are displayed. All parameters are age standardised.

6.3.3.5 Objective 1: Fatigue negatively impacts focus more in fibromyalgia

Higher fatigue levels during the task were demonstrated a relatively weak, but significant correlation, with greater RT variability across the cohort (**Figure 6-6E**; r=0.22, p<0.001). This relationship was stronger in the fibromyalgia group (FM: r=0.32, p=0.01) compared to healthy controls (HC: r=0.13, p=0.086), with a significant group-by-fatigue interaction (F=10.72, p=0.0012).

Fatigue was also modestly associated with poorer performance on other NVT metrics, including lower hit rates (**Figure 6A**; r=-0.16, p=0.011), higher false alarm rates (**Figure 6-6B**; r=0.15, p=0.015), and lower sensitivity (**Figure 6-6C**; r=-0.18, p=0.0036), although no significant group-by-fatigue interactions were observed for these outcomes. RT was not correlated with fatigue in either group (**Figure 6-6D**; r=-0.06, p=0.34).

These results suggest that fibromyalgia patients are more susceptible to the negative impact of fatigue on focus, as indicated by RT variability, while the effects of fatigue on accuracy and errors are similar across groups.

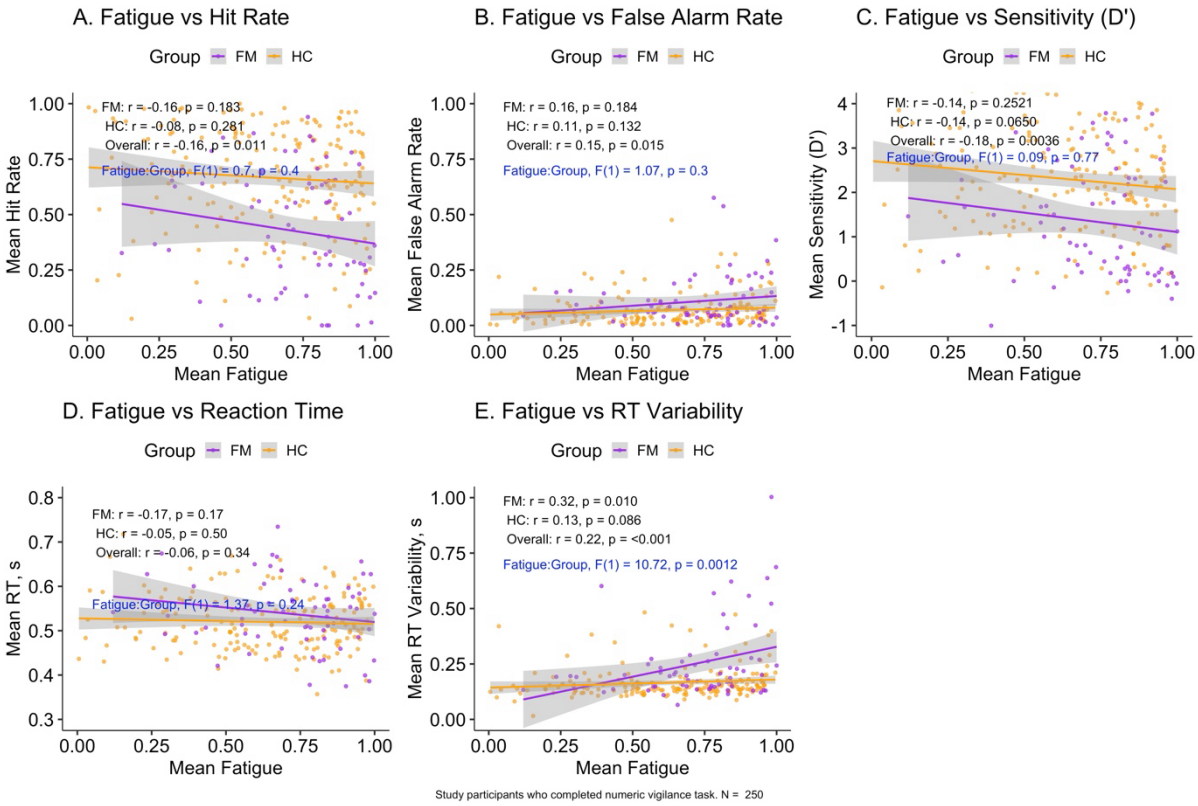


Figure 6-6. Fatigue negatively impacts focus more in fibromyalgia

Relationships between fatigue and NVT performance metrics are displayed for fibromyalgia (FM) patients and healthy controls (HCs). Across all participants, higher fatigue levels were associated with worse performance, including lower hit rates (A), higher false alarm rates (B), lower sensitivity (C), and greater reaction time variability (E). There was no significant overall relationship between fatigue and reaction time (D). fibromyalgia patients demonstrated a significantly stronger relationship between fatigue and reaction time variability (E; interaction: F(1)=10.72, p=0.0012), indicating heightened sensitivity of focus to fatigue in this group. No significant interactions between fatigue and group were observed for other performance metrics. Fatigue is measured on a visual analogue scale, with higher values indicating worse fatigue. Regression slopes with 95% confidence intervals are shown for each group. Pearson's correlation coefficients (r) and p-values are annotated for FM, HC, and the overall cohort, alongside ANOVA interaction F and p-values. FM, fibromyalgia; HC, healthy control.

6.3.3.6 Objective 1: Greater motivation improves focus more in fibromyalgia

Higher motivation levels were moderately associated with lower RT variability across the cohort (**Figure 6-7E**; r=-0.30, p<0.001), with a stronger effect in fibromyalgia patients (FM: r=-0.36, p=0.0028) than in healthy controls (HC: r=-0.19, p=0.0096). A significant group-by-motivation interaction (F=13.39, p<0.001) indicated that fibromyalgia patients showed heightened sensitivity to motivation in maintaining focus compared to controls.

Greater motivation was also moderately correlated with better performance across other metrics, including higher hit rates (**Figure 6-7A**; r=0.39, p<0.001), lower false alarm rates (**Figure 6-7B**; r=-0.24, p<0.001), and greater sensitivity (**Figure 6-7C**; r=0.38, p<0.001). However, no group-by-motivation interactions were observed for these outcomes, suggesting similar relationships across groups. RT was not significantly correlated with motivation in either group (**Figure 6-7D**; r=-0.1, p=0.14).

These findings highlight that while greater motivation benefits all participants, fibromyalgia patients exhibit a heightened dependency on motivation to sustain focus, reflected in RT variability.

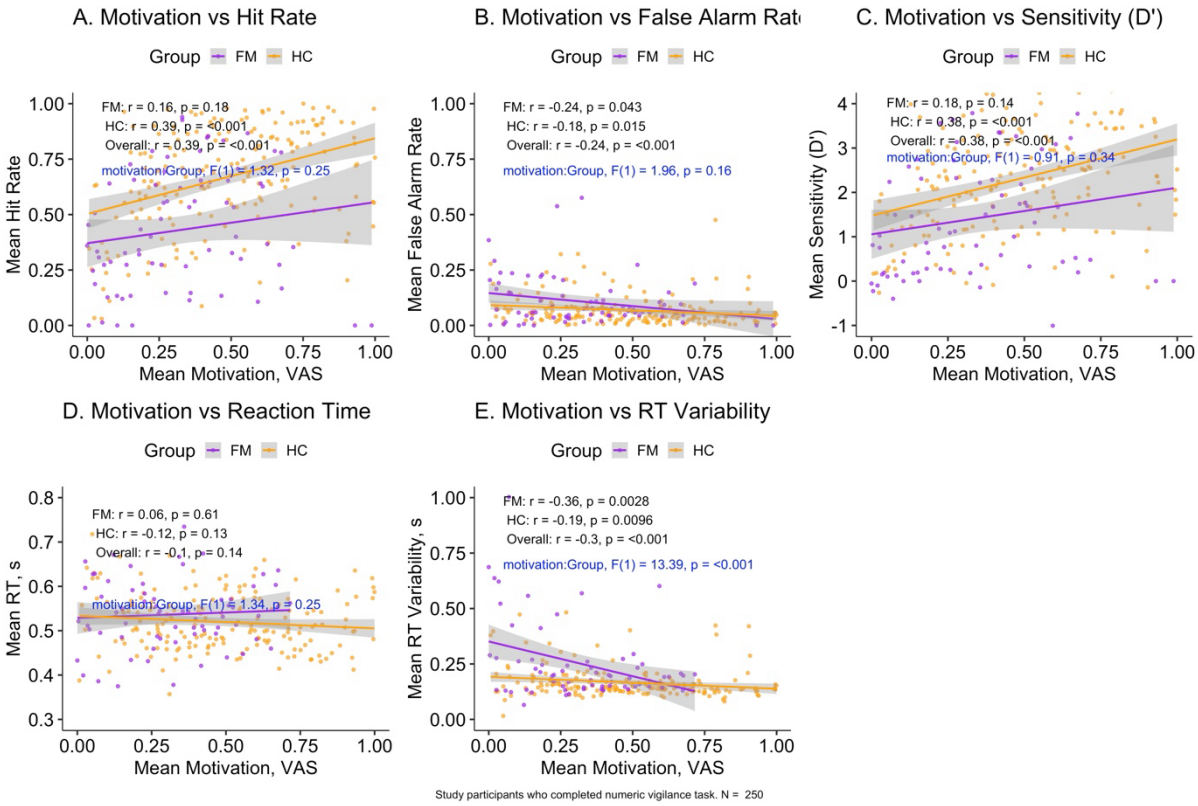


Figure 6-7. Greater motivation improves focus more in fibromyalgia.

Relationships between motivation and NVT performance metrics are displayed for fibromyalgia (FM) patients and healthy controls (HCs). Across all participants, higher motivation levels were associated with better performance, including higher hit rates (A), lower false alarm rates (B), higher sensitivity (C), and lower reaction time variability (E). There was no significant overall relationship between motivation and reaction time (D). fibromyalgia patients demonstrated a significantly stronger relationship between motivation and reaction time variability (E; interaction: $F(1)=13.39$, $p<0.001$), indicating heightened sensitivity of focus to motivation in this group. No significant interactions between motivation and group were observed for other performance metrics. Motivation is measured on a visual analogue scale, with higher values indicating greater motivation. Regression slopes with 95% confidence intervals are shown for each group. Pearson's correlation coefficients (r) and p-values are annotated for FM, HC, and the overall cohort, alongside ANOVA interaction F and p-values. FM, fibromyalgia; HC, healthy control.

6.3.4 Objective 2: Fibromyalgia symptom severity, particularly pain intensity and sleep disturbances, associated with sustained attention performance

6.3.4.1 Objective 2: Fibromyalgia severity associated with worse focus and accuracy

Worse fibromyalgia symptom severity (FIQR) was associated with impaired task performance, specifically greater RT variability (**Figure 6-8B**; P=0.004) and worse d' (**Figure 6-8C**; P=0.03). There was no significant relationship between FIQR scores and RT (**Figure 6-8A**; P=0.22). After adjusting for education, employment status, and analgesia use, these associations were attenuated but remained significant. FIQR accounted for 11.7% of the variance in RT variability and 3.8% in D'. These results suggest that more severe fibromyalgia symptoms exert a modest impact on attentional focus and accuracy during the task.

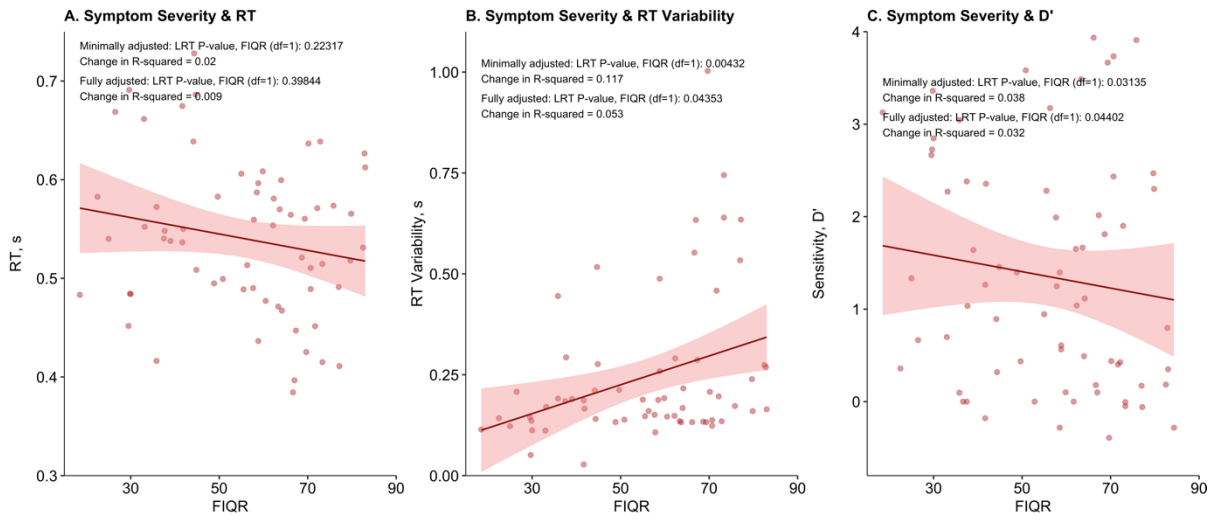


Figure 6-8. Fibromyalgia severity associated with worse focus and accuracy.

Relationships between fibromyalgia symptom severity on the FIQR and NVT performance metrics are displayed for fibromyalgia patients. Worse symptom severity is associated with greater RT variability (B) and more errors (C). There was no significant relationship with reaction time (A). fibromyalgia symptom severity measured with the FIQR, with higher values indicating worse symptoms. Minimally adjusted model includes age and sex. Fully adjusted model includes education (degree, no degree), employment status (employed, not employed), and analgesia use (opioids, tricyclic antidepressants, or gabapentinoids). Regression slopes with 95% confidence intervals are shown. Likelihood ratio test (LRT) p-values and changes in R^2 are provided for the contribution of FIQR in the models. FIQR, Fibromyalgia Impact Questionnaire–Revised; s, second; FM, fibromyalgia; LRT, likelihood ratio test; df, degrees of freedom.

6.3.4.2 Objective 2: Pain and motivation independently impact focus and accuracy in fibromyalgia

Baseline pain, fatigue, and motivation levels were analysed for their independent contributions to focus (RT variability) and accuracy (d'). Pain negatively influenced both focus (**Figure 6-9A,** β=0.23 for each 1-point increase in pain VAS; 95% CI 0.027, 0.43; P=0.027) and accuracy (**Figure 6-9B,** β=-0.22; 95% CI -0.39, -0.052; P=0.01). Conversely, motivation was associated with improved focus (**Figure 6-9A,** β=-0.34, 95% CI -0.54, -0.15; P=0.0006), but showed no significant relationship with accuracy (**Figure 6-9B)**. Fatigue did not independently influence either focus or accuracy after accounting for pain and motivation (**Figure 6-9A&B)**. Further details, including full statistical results and figures, are provided in Appendix E. These results suggest that pain impairs focus and accuracy, while motivation mitigates deficits in focus but not accuracy. Fatigue had no significant independent impact.

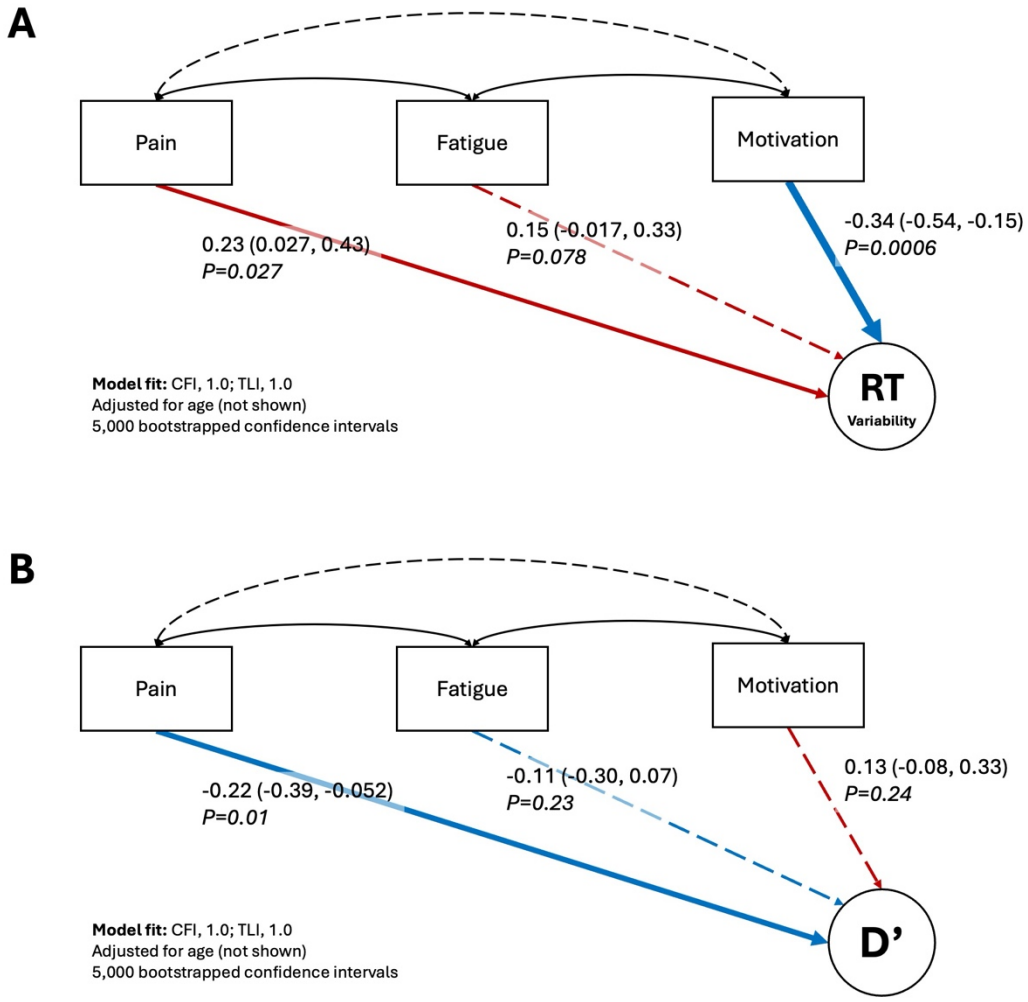


Figure 6-9. Pain and Motivation Independently Impact Focus (A) and Accuracy (B) in Fibromyalgia

Both pain and motivation, but not fatigue, were independently associated with focus (A). Only pain, but not fatigue or motivation, was independently associated with accuracy (B). Structural equation modelling was performed, adjusting for age (not shown for clarity), with 5,000 bootstrapped confidence intervals and P-values reported. Standardised parameter estimates and their 95% confidence intervals are displayed along the pathways. Red solid lines indicate significant positive associations, blue solid lines indicate significant negative associations, and dotted lines represent non-significant pathways. Covariances between pain, fatigue, and motivation were modelled. Model fit was excellent (CFI=1.0; TLI=1.0). Abbreviations: RT, reaction time; NVT, numeric vigilance task; CFI, comparative fit index; TLI, Tucker-Lewis index; VAS, visual analogue scale.

6.3.4.3 Objective 2: Pain intensity and neuropathic features impair focus and accuracy

Focus was significantly impaired by baseline pain intensity (**Figure 6-10A,** β=0.27 for each 1-point increase in pain VAS; 95% CI 0.014, 0.54; P=0.039) and neuropathic pain (**Figure 6-10A**, β=0.33; 95% CI 0.05, 0.61; P=0.022), while widespread pain showed no effect (**Figure 6-10A**). Accuracy was negatively impacted by pain intensity (**Figure 6-10B,** β=-0.28; 95% CI -0.45, -0.12; P<0.001) and neuropathic pain (**Figure 6-10B,** β=-0.18; 95% CI -0.36, -0.01; P=0.038), but counterintuitively improved by widespread pain (**Figure 6-10B,** β=0.18; 95% CI 0.01, 0.36; P=0.038). Further details are in Appendix E (Section E.6.1). This suggests that features of pain which may interrupt attention, such as intensity of pain or neuropathic features, but not how widespread the pain is, negatively impacts both focus and accuracy.

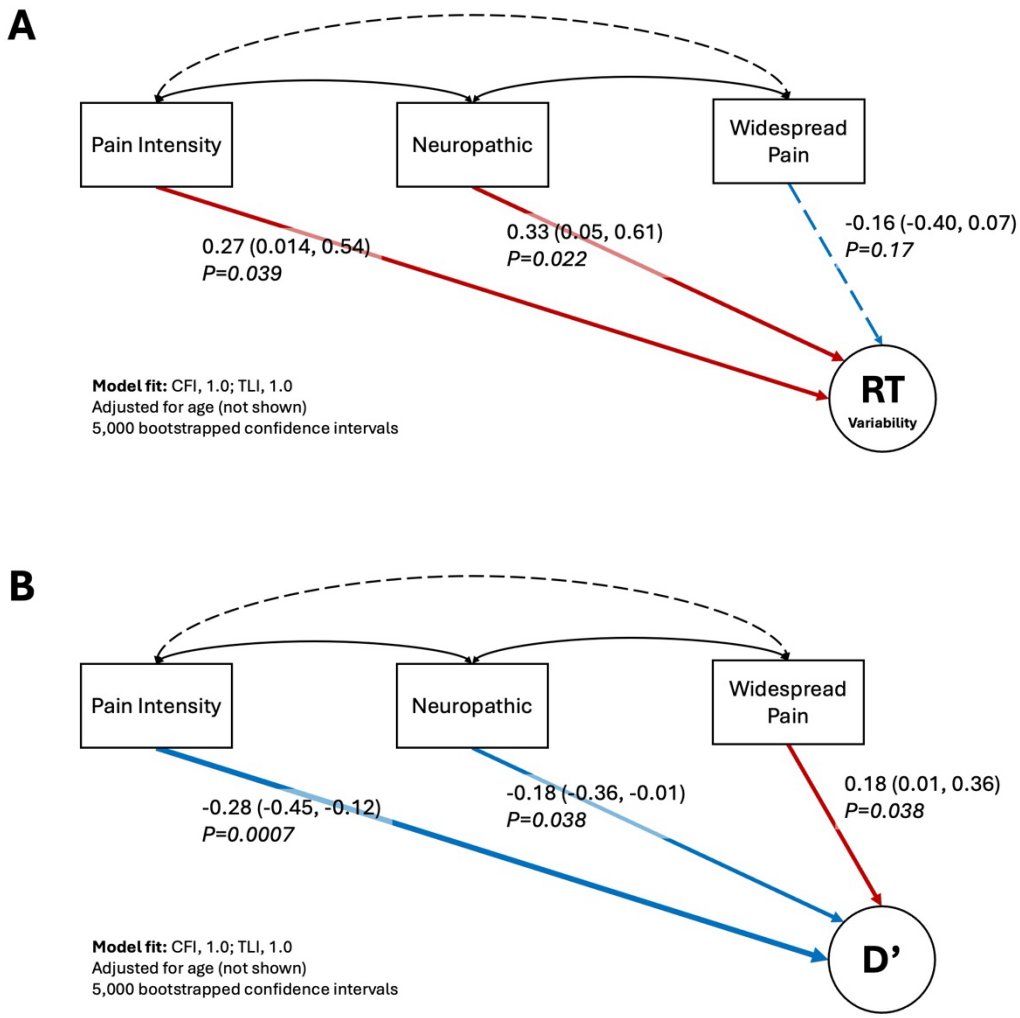


Figure 6-10. Pain intensity and neuropathic features impair focus (A) and accuracy (B)

Both pain intensity and neuropathic symptoms, but not widespread pain, were independently associated with worse focus (A), and accuracy (B). Pain intensity measured using a VAS. Neuropathic pain measured using the PainDETECT questionnaire. Widespread pain measuring using widespread pain index (WPI). Structural equation modelling was performed, adjusting for age (not shown for clarity), with 5,000 bootstrapped confidence intervals and P-values reported. Standardised parameter estimates and their 95% confidence intervals are displayed along the pathways. Red solid lines indicate significant positive associations, blue solid lines indicate significant negative associations, and dotted lines represent non-significant pathways. Covariances between pain intensity, neuropathic pain, and widespread pain were modelled. Model fit was excellent (CFI=1.0; TLI=1.0). Abbreviations: RT, reaction time; NVT, numeric vigilance task; CFI, comparative fit index; TLI, Tucker-Lewis index. VAS, visual analogue scale.

6.3.4.4 *Objective 2: Baseline pain impairs accuracy and focus without affecting rate of decline*

Higher baseline pain was associated with poorer task performance, reflected in lower hit rates (**Figure 6-11A**; F=4.67, p=0.034), reduced D' (**Figure 6-11C**; F=4.25, p=0.042), and greater RT variability (**Figure 6-11E**; F=4.28, p=0.042). These effect sizes were relatively modest, and were consistent across the task, with no significant pain-by-time interactions, indicating that baseline pain affects accuracy and focus but not their rate of decline over time. Baseline pain was not significantly associated with false alarm rate (**Figure 6-11**B; F=2.13, p=0.149), RT (**Figure 6-11D**; F=0.16, p=0.686), or their changes over time.

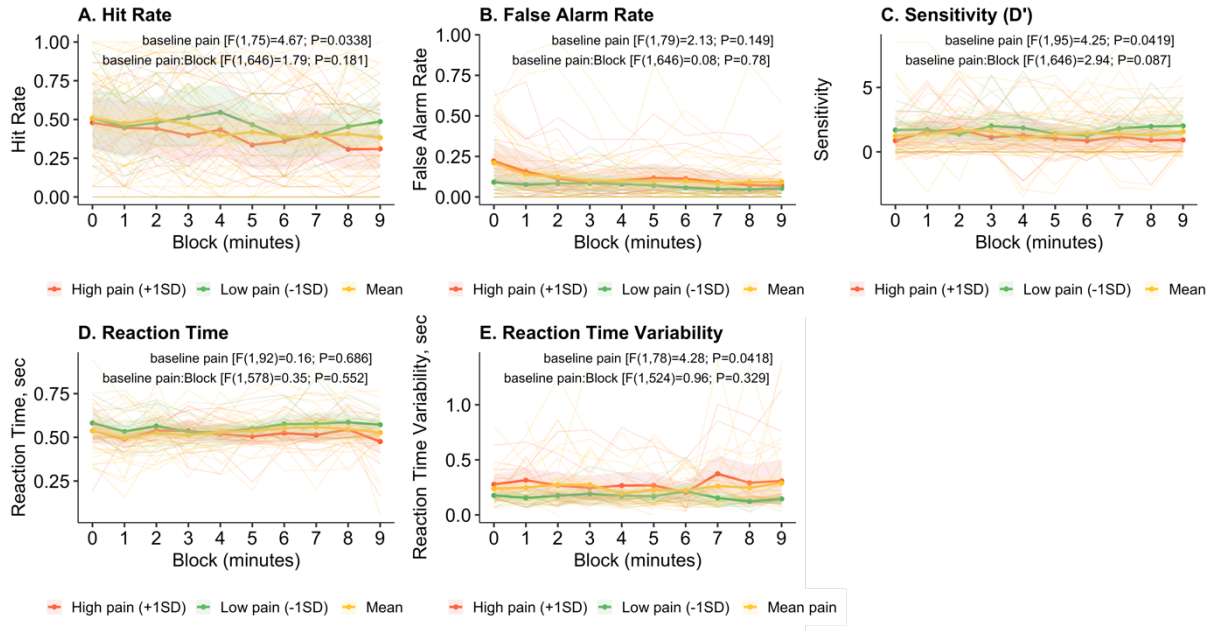


Figure 6-11. Baseline pain impairs accuracy and focus without affecting rate of decline

Linear mixed models examining the association between baseline pain intensity and NVT performance are shown. Results for the main effect of baseline pain (continuous variable) and pain-by-time (block) interactions are annotated. Individual trajectories and mean (±1 SD) values with 95% confidence intervals are displayed for participants grouped by baseline pain (mean ±1 SD). Higher baseline pain was associated with lower hit rate (A) and sensitivity (C), and greater RT variability (E). There were no significant pain-by-time interactions, suggesting baseline pain does not impact the rate of change in focus. Models were adjusted for age, sex, education, employment status, and analgesia use (opioids, tricyclic antidepressants, and gabapentinoids). FM, fibromyalgia; SD, standard deviation.

6.3.4.5 Objective 2: Brain-fog and affect show limited impact on sustained attention

Brain-fog and affective symptoms had limited associations with task performance (**Figure 6-12**). Brain-fog was linked to a small increase in RT variability in the minimally adjusted model (ΔR^2 = 9%; LRT p=0.012) but this was attenuated after adjusting for socio-demographics and medication use (ΔR^2 = 4.8%; LRT p=0.055). No significant associations were observed between brain-fog and RT (ΔR^2 = 2%; LRT P=0.21) or D' (ΔR^2 = 2.2%; LRT P=0.10). This suggests a disconnect between subjective and objective cognitive performance.

Depressive symptoms demonstrated a small association with worse focus (**Figure 6-12E**, ΔR^2 = 5.6%; LRT p=0.048) and task accuracy (**Figure 6-12F**, ΔR^2 = 4.8%; LRT p=0.032) but were attenuated after full adjustment (focus: ΔR^2 = 2.3%; LRT p=0.18. Accuracy: ΔR^2 = 2.9%; LRT p=0.052). Anxiety symptoms were not significantly associated with focus or accuracy (LRT p>0.05 for all, **Figure 6-12G-I**). Overall, these symptoms explained little variance in task performance (<5% ΔR^2), except brain-fog in the minimally adjusted model, which accounted for 9% of variance in RT variability.

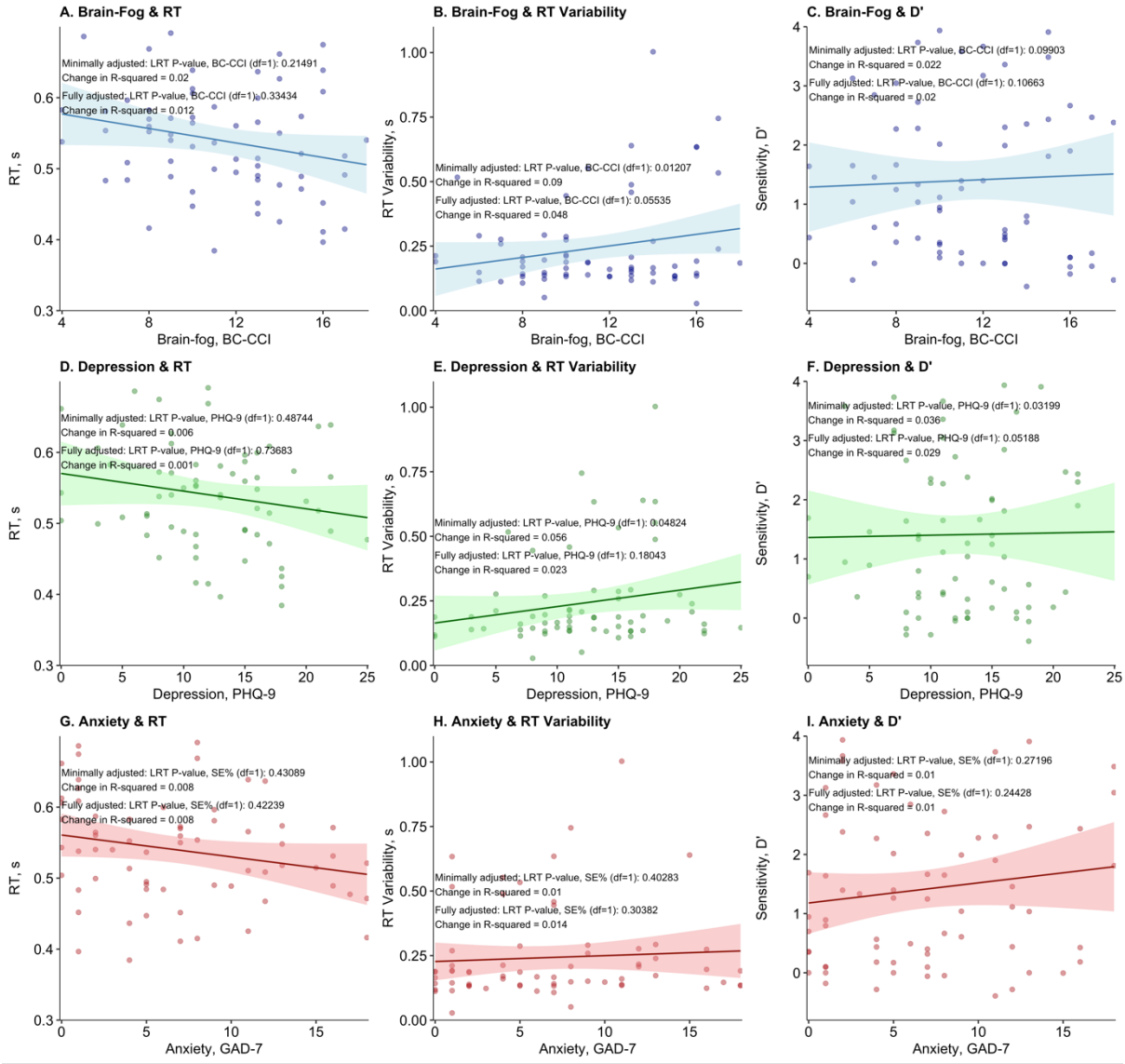


Figure 6-12. Brain-fog and affect show limited impact on sustained attention.

Relationships between levels of brain-fog (A-C), depression (D-F), and anxiety (G-I) symptoms at baseline and subsequent NVT performance metrics are displayed for fibromyalgia patients. Worse brain-fog symptoms associated with worse focus (greater RT variability, C). Worse depression symptoms associated with worse focus (E) and accuracy (F). There was no significant relationship with reaction time for brain-fog or depression. Anxiety symptoms were not associated with task performance. Brain-fog measured with BC-CCI; depressive symptoms measured using PHQ-9; anxiety symptoms assessed with GAD-7. Higher values on all measures indicate worse symptoms. Minimally adjusted model includes age and sex. Fully adjusted model includes education (degree, no degree), employment status (employed, not employed), and analgesia use (opioids, tricyclic antidepressants, or gabapentinoids). Training blocks omitted. Regression slopes with 95% confidence intervals are shown. Likelihood ratio test (LRT) p-values and changes in R^2 are provided for the contribution of symptom severity in the models. BC-CCI, British Columbia Cognitive Complaints Inventory; PHQ-9, Patient health questionnaire 9-item; GAD-7, Generalised anxiety disorder 7-item; RT, reaction time; s, second; FM, fibromyalgia; LRT, likelihood ratio test; df, degrees of freedom.

6.3.4.6 Objective 2: Poor sleep quality is associated with worse sustained attention

Sleep quality was consistently associated with focus and accuracy during the NVT (**Figure 6-13**). Worse insomnia symptoms, measured by ISI, demonstrated small-to-moderate associations with worse focus (LRT p=0.024, ΔR^2=7.3%) and accuracy (LRT p=0.0047, ΔR^2=6.1%) in both minimally and fully adjusted models, but not with RT (P=0.27, ΔR^2=2.3%). Non-linear associations between TST and task performance revealed that both short (<6 hours) and long (>8 hours) TST impaired performance. These deviations displayed a moderate-to-strong relationship with slower RT (LRT p=0.028, ΔR^2=9.3%), worse focus (LRT p=0.002, ΔR^2=17.3%), and poorer accuracy (LRT p=0.015, ΔR^2=7.0%). Similarly, short and long time in bed also displayed a moderate-to-strong relationship with worse focus (LRT p<0.001, ΔR^2=21.3%) and accuracy (LRT p=0.008, ΔR^2=7.6%). While greater sleep efficiency was associated with faster RT (LRT p=0.029, ΔR^2=6.3%), it did was not significantly associated with focus or accuracy (P>0.05). These relationships remained significant after adjusting for socio-demographics and analgesia use, indicating a robust impact of sleep quality on task performance.

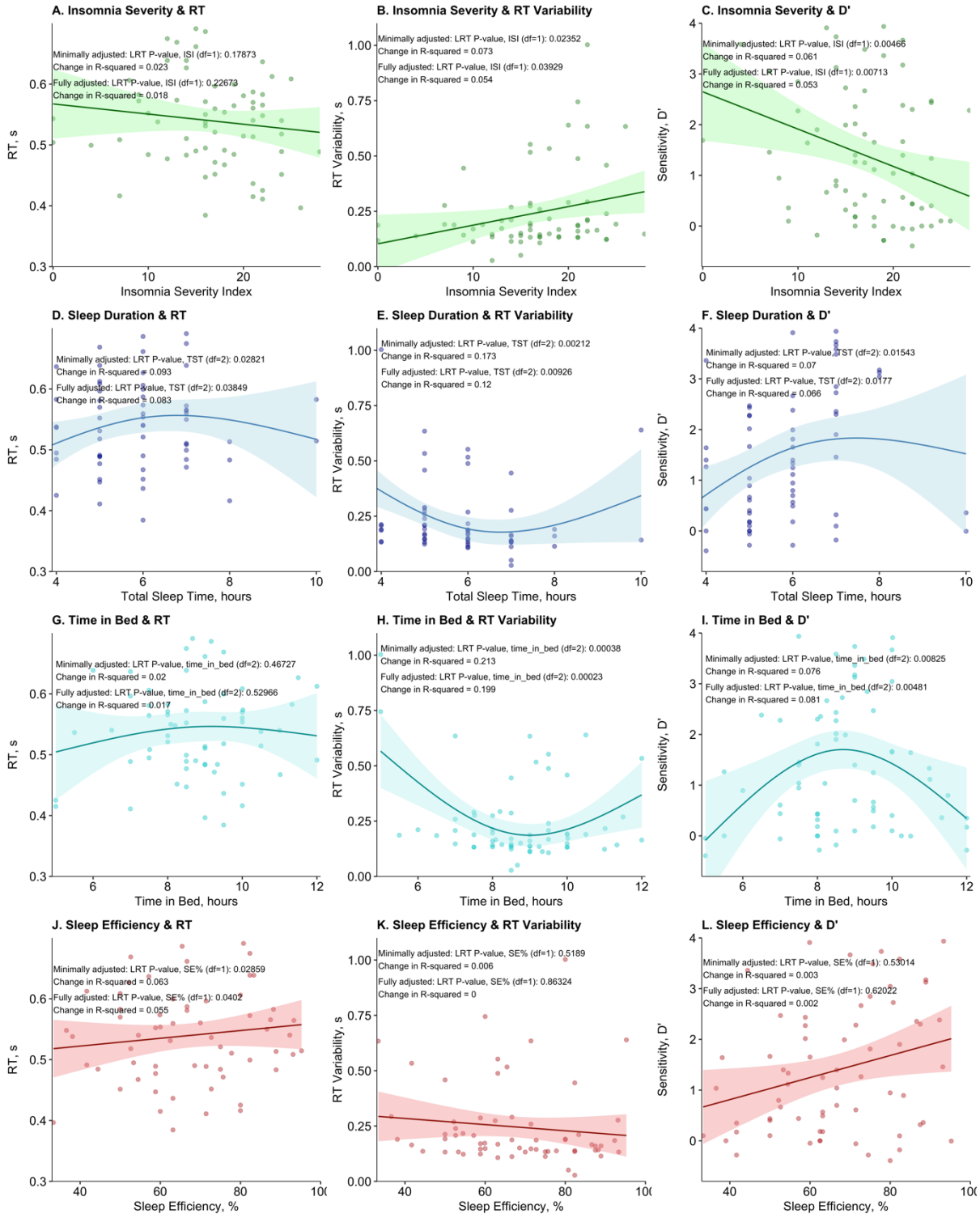


Figure 6-13. Poor sleep quality is associated with worse sustained attention

Relationships between insomnia symptom severity (A-C), sleep duration (D-F), time in bed (G-I), and sleep efficiency at baseline and subsequent NVT performance metrics are displayed for fibromyalgia patients. Worse insomnia symptoms associated with worse focus (greater RT variability, B) and accuracy (Sensitivity, C). Self-reported total sleep time displayed a non-linear relationship with speed (RT, D), focus (RT variability, E), and accuracy (sensitivity, F). Time in bed displayed a similar relationship with focus (RT, H) and accuracy (Sensitivity, I). Greater sleep efficiency was associated with faster RT (J) but not focus or accuracy. Insomnia symptoms measured using ISI, where higher scores indicate worse symptoms. Sleep duration (total sleep time), time in bed, and sleep efficiency are self-reported and derived from the Pittsburgh Sleep Quality Index (PSQI). Minimally adjusted model includes age and sex.

Fully adjusted model includes education (degree, no degree), employment status (employed, not employed), and analgesia use (opioids, tricyclic antidepressants, or gabapentinoids). Training blocks omitted. Regression slopes with 95% confidence intervals are shown. Likelihood ratio test (LRT) p-values and changes in R^2 are provided for the contribution of symptom severity in the models. ISI, Insomnia Severity Index; RT, reaction time; s, second; FM, fibromyalgia; LRT, likelihood ratio test; df, degrees of freedom.

6.3.4.7 Objective 2: Abnormal sleep duration impairs focus

SEM was used to evaluate the independent contributions of insomnia severity, TST and time in bed to focus (RT variability) and accuracy (d') during the NVT (**Figure 6-14**). Abnormal TST was moderately associated with worse focus (**Figure 6-14A,** β=0.20; 95% CI 0.01, 0.40; P=0.044), while no significant associations were found for insomnia severity or time in bed (P >0.05 for both).

Accuracy (d') was not independently associated with any of the sleep characteristics (**Figure 6-14B,** P>0.05 for all). These findings suggest that short or long TST negatively impacts focus. Insomnia severity and time in bed, in contrast, displayed no significant effect on either measure after accounting for other sleep characteristics.

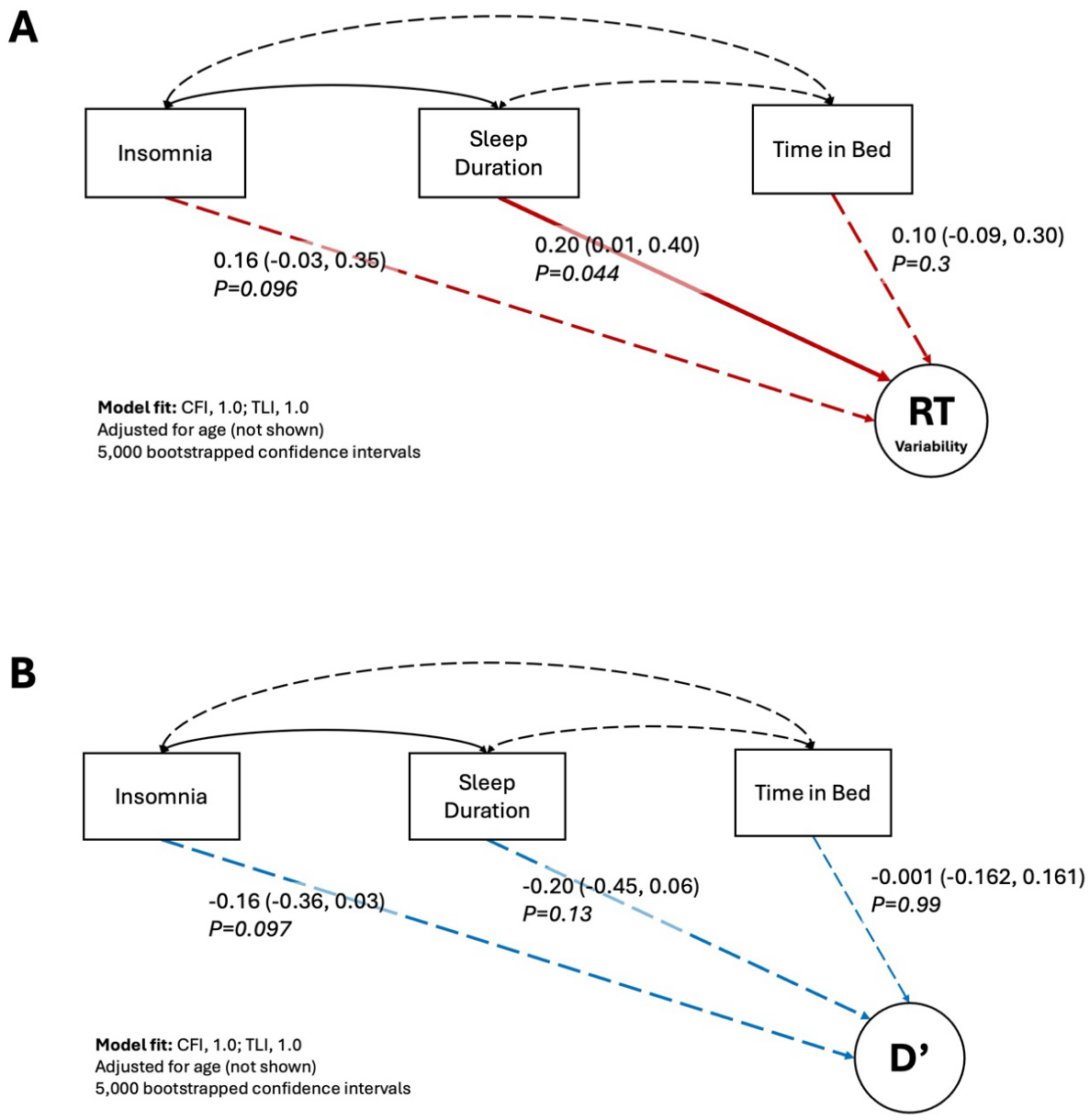


Figure 6-14. Abnormal sleep duration impairs focus, while insomnia and time in bed show no independent effects

Abnormal sleep duration was independently associated with worse focus (A). No sleep characteristic was independently associated with accuracy (B). Insomnia measured with Insomnia Severity Index. Sleep duration and time in bed measured using PSQI and modelled as binary variables for <6 or >9 hours, to account for non-linear association. Structural equation modelling was performed, adjusting for age (not shown for clarity), with 5,000 bootstrapped confidence intervals and P-values reported. Standardised parameter estimates and their 95% confidence intervals are displayed along the pathways. Red solid lines indicate significant positive associations, blue solid lines indicate significant negative associations, and dotted lines represent non-significant pathways. Covariances between pain intensity, neuropathic pain, and widespread pain were modelled. Model fit was excellent (CFI=1.0; TLI=1.0). Abbreviations: RT, reaction time; NVT, numeric vigilance task; CFI, comparative fit index; TLI, Tucker-Lewis index.

6.3.4.8 Objective 2: FIQR impacts focus directly, but impacts accuracy through pain severity

FIQR exerted a strong total effect on focus (**Figure 6-15A**; β=0.36, 95%CI 0.16, 0.60; P<0.001), primarily through direct pathways (β=0.22, 95%CI 0.01, 0.43; P=0.044). While indirect pathways via pain and sleep contributed to 41.6% of this effect, both the individual and combined indirect effects were weak and non-significant (β=0.15, 95%CI -0.004, 0.38; P=0.135).

In contrast, the effect of FIQR on accuracy was fully mediated through pain and sleep pathways (**Figure 6-15B**). The total effect (β=-0.19, 95%CI -0.34, -0.04; P=0.013) was driven by pain intensity (β=-0.13, 95%CI -0.25, -0.04; P=0.021), with sleep having a smaller, non-significant contribution (β=-0.048, 95% CI -0.14, 0.003; P=0.18). The direct effect was negligible (β=-0.013, 95% CI -0.18, 0.016; P=0.88).

These results highlight that while symptom severity impairs accuracy via pain-related mechanisms, its effect on focus may involve pathways independent of pain and sleep disturbances.

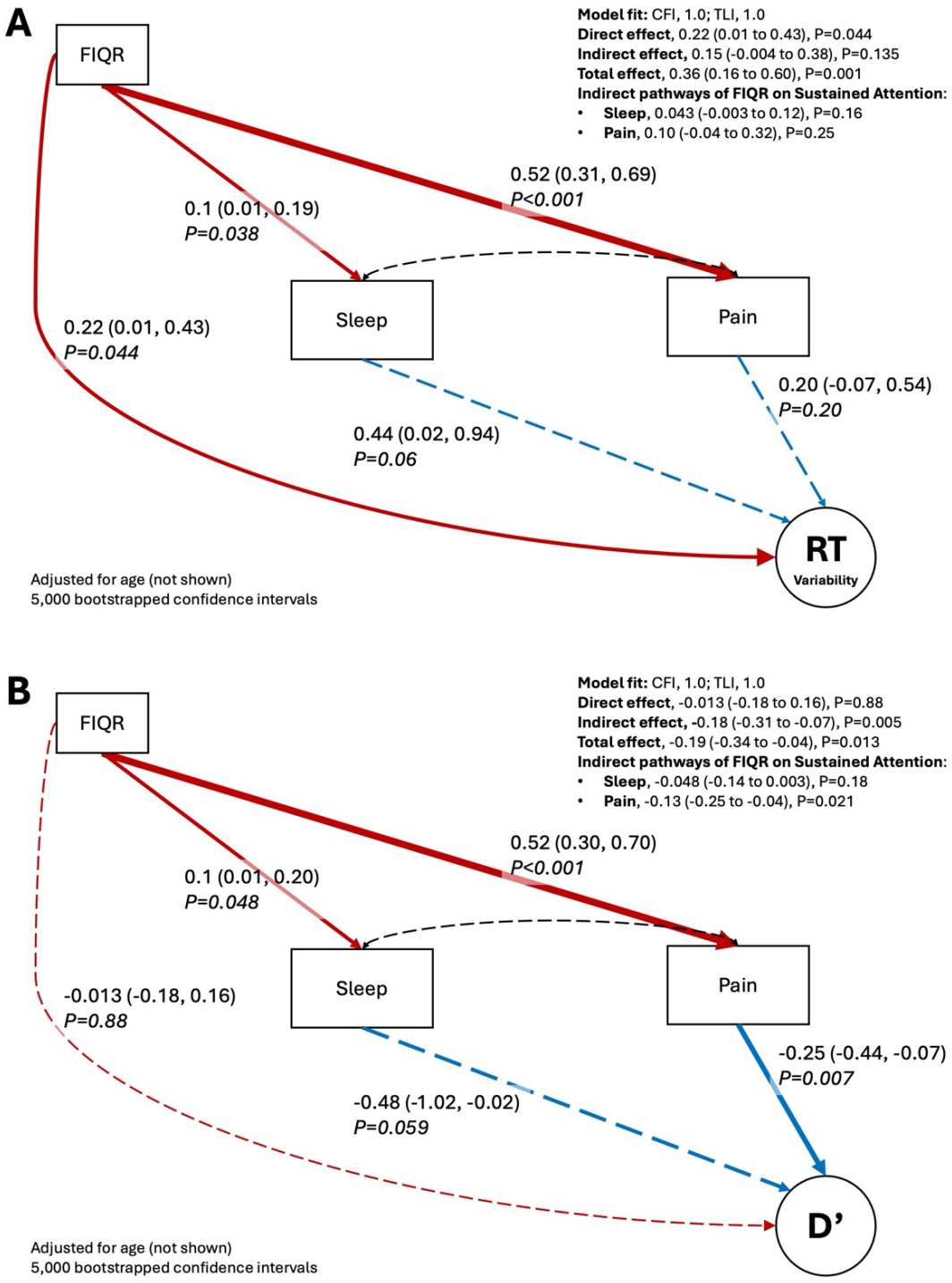


Figure 6-15. FIQR impacts focus directly, but impacts accuracy through pain severity

Sustained attention measured using task sensitivity (d'). Sleep is TST <6 or >9 hours. Pain is Pain intensity VAS at baseline. Structural equation modelling was performed, adjusting for age (not shown for clarity), with 5,000 bootstrapped confidence intervals and P-values reported. Standardised parameter estimates and their 95% confidence intervals are displayed along the pathways. Red solid lines indicate significant positive associations, blue solid lines indicate significant negative associations, and dotted lines represent non-significant pathways. Covariances between pain and sleep were modelled. Model fit was excellent (CFI=1.0; TLI=1.0). Abbreviations: RT, reaction time; NVT, numeric vigilance task; CFI, comparative fit index; TLI, Tucker-Lewis index. FIQR, fibromyalgia impact questionnaire revised. TST, total sleep time

6.3.4.9 Objective 2: Analgesia use & sustained attention

The impact of current analgesia use and the number of medications on sustained attention is detailed in Appendix E (Section E.6.2), with no significant associations observed between analgesia use (opioids, TCAs, gabapentinoids) or medication count and NVT performance metrics.

6.3.5 Objective 3: Explore neural correlates of sustained attention deficits in fibromyalgia using resting-state functional connectivity analyses

Fifty-five patients from the PainLESS study with rs-fMRI and NVT data were included in imaging analyses. Baseline characteristics were broadly similar to those without brain imaging (Supplementary Table E-2).

6.3.5.1 Objective 3: PAG-amygdala connectivity associated with speed-accuracy trade-offs in fibromyalgia

PAG-amygdala resting state functional connectivity (RSFC) demonstrated a significant, and relatively strong, U-shaped relationship with performance on the NVT in fibromyalgia (**Figure 6-16**). Both high and low PAG-Amygdala RSFC demonstrated a strong association with more errors (false alarm rate, **Figure 6-16B**; LRT p=0.0018, ΔR^2 20.2%), with only slight attenuation after adjustment for socio-demographics and medication use (LRT p=0.0025, ΔR^2 16.5%). Similarly, both extremes of RSFC were strongly associated with worse focus (RT variability, **Figure 6-16D**; LRT p=0.017, ΔR^2 15.2%), modestly attenuated in the fully adjusted model (LRT p=0.036, ΔR^2 10.7%).

Interestingly, high and low RSFC levels were also strongly associated with faster reaction times (**Figure 6-16C**; LRT p=0.0015, ΔR^2 17.7%), which remained robust in the fully adjusted model (LRT p=0.0005, ΔR^2 18.4%). However, no meaningful associations were observed with task accuracy, including hit rate and d' (**Figure 6-16A&E**; LRT p>0.05 for both).

These findings suggest that fibromyalgia patients with either increased or decreased PAG-amygdala connectivity exhibit faster but more variable RTs, resulting in more errors.

6.3.5.2 Objective 3: PAG-amygdala connectivity associated with sleep, but not other symptoms

PAG-amygdala RSFC showed no meaningful associations with pain, fatigue, motivation (**Figure 6-17A-C**; LRT P>0.05 for all), brain-fog, depression, or anxiety (**Figure 6-18A-C**; LRT P>0.05 for all). However, there was a significant, and strong, non-linear U-shaped relationship with several sleep measures. Both increased and decreased PAG-amygdala RSFC were associated with longer time in bed (**Figure 6-19C**; LRT P=0.007, ΔR^2=14.4% in fully adjusted model) and lower sleep efficiency (**Figure 6-19D**; LRT P=0.04, ΔR^2=9.3%). No associations were found with insomnia severity or TST (**Figure 6-19A&B**; P>0.05). These findings suggest that PAG-amygdala connectivity is associated with sleep behaviours in fibromyalgia through non-linear mechanisms.

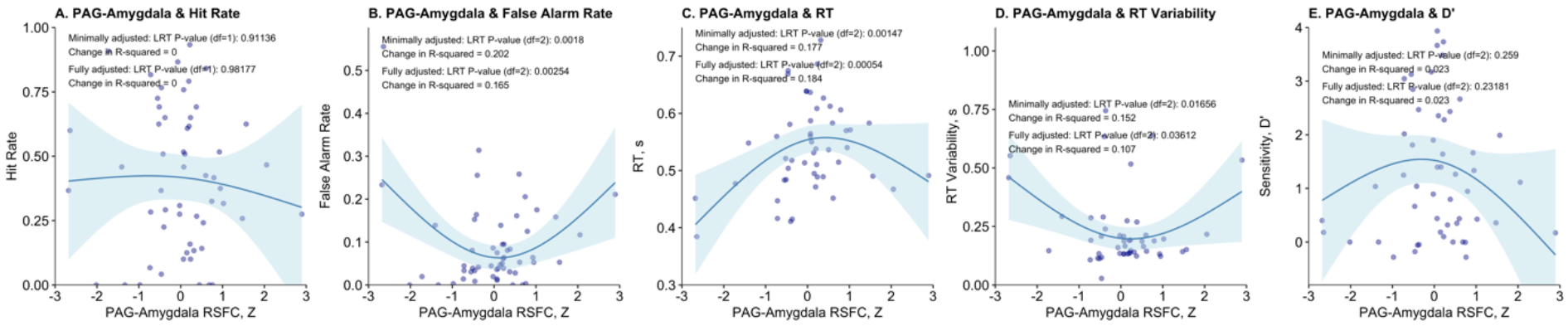


Figure 6-16. PAG-amygdala connectivity associated with speed-accuracy trade-offs in fibromyalgia.

Relationships between PAG-amygdala resting state functional connectivity (RSFC) and NVT performance metrics are displayed for fibromyalgia patients. Both lower and higher PAG-amygdala RSFC is associated with more errors (false alarm rate, B), faster speed (RT, C), and worse focus (greater RT variability, D). There was no significant association with correct responses (hit rate, A) or overall task accuracy (sensitivity, E). RSFC measured during rs-fMRI during baseline visit, and modelled using second-order polynomial term to account for non-linear association. Minimally adjusted model includes age and sex. Fully adjusted model includes education (degree, no degree), employment status (employed, not employed), and analgesia use (opioids, tricyclic antidepressants, or gabapentinoids). Training blocks omitted. Regression slopes with 95% confidence intervals are shown. Likelihood ratio test (LRT) p-values and changes in R^2 are provided for the contribution of PAG-Amygdala RSFC in the models. RSFC, resting state functional connectivity; RT, reaction time; s, second; FM, fibromyalgia; LRT, likelihood ratio test; df, degrees of freedom.

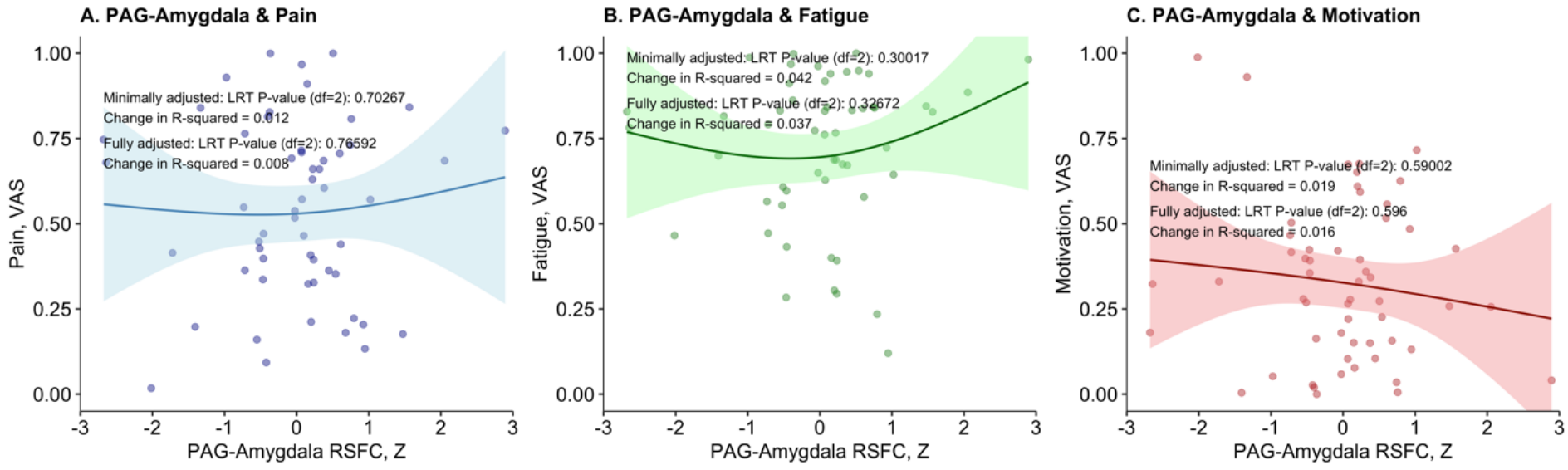


Figure 6-17. PAG-amygdala functional connectivity is not associated with pain, fatigue, or motivation during the NVT.

Relationships between PAG-amygdala resting state functional connectivity (RSFC) and self-reported levels of pain (A), fatigue (B), and motivation (C) during the NVT are displayed for fibromyalgia patients. PAG-amygdala RSFC is not associated with behaviour. RSFC measured during rs-fMRI during baseline visit, and modelled using second-order polynomial term to account for non-linear association. Minimally adjusted model includes age and sex. Fully adjusted model includes education (degree, no degree), employment status (employed, not employed), and analgesia use (opioids, tricyclic antidepressants, or gabapentinoids). Training blocks omitted. Regression slopes with 95% confidence intervals are shown. Likelihood ratio test (LRT) p-values and changes in R^2 are provided for the contribution of PAG-Amygdala RSFC in the models. RSFC, resting state functional connectivity; FM, fibromyalgia; LRT, likelihood ratio test; df, degrees of freedom.

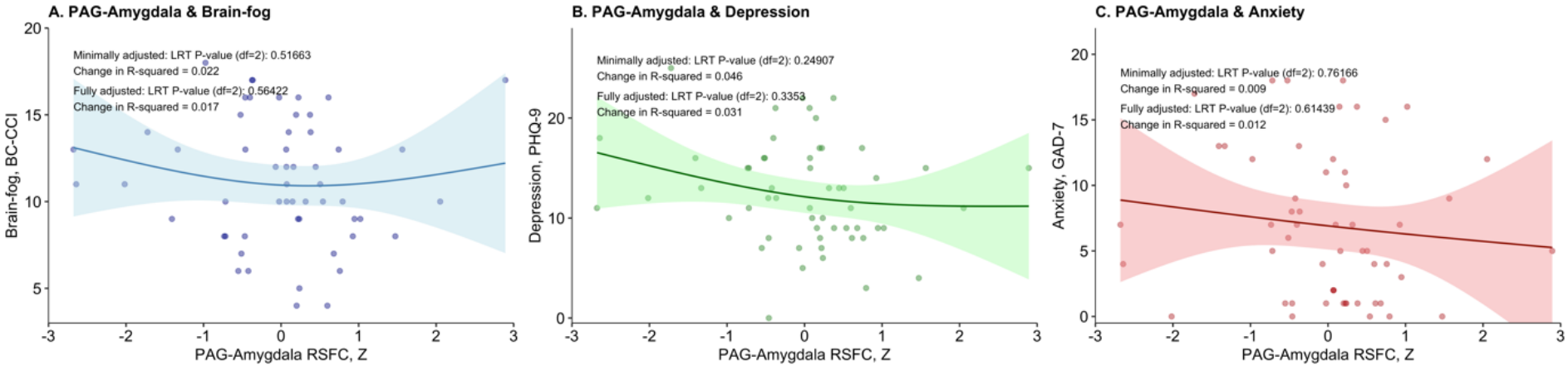


Figure 6-18. PAG-amygdala functional connectivity is not associated with brain-fog or affect in fibromyalgia.

Relationships between PAG-amygdala resting state functional connectivity (RSFC) and brain-fog (A), depression (B), and anxiety (C) symptom severity are displayed for fibromyalgia patients. PAG-amygdala RSFC is not associated with severity of these symptoms. RSFC measured during rs-fMRI during baseline visit, and modelled using second-order polynomial term to account for non-linear association. Minimally adjusted model includes age and sex. Fully adjusted model includes education (degree, no degree), employment status (employed, not employed), and analgesia use (opioids, tricyclic antidepressants, or gabapentinoids). Training blocks omitted. Regression slopes with 95% confidence intervals are shown. Likelihood ratio test (LRT) p-values and changes in R^2 are provided for the contribution of PAG-Amygdala RSFC in the models. RSFC, resting state functional connectivity; FM, fibromyalgia; BC-CCI, British Columbia cognitive complaints inventory; PHQ-9, patient health questionnaire 9-item; GAD-7, generalised anxiety disorder 7-item; LRT, likelihood ratio test; df, degrees of freedom.

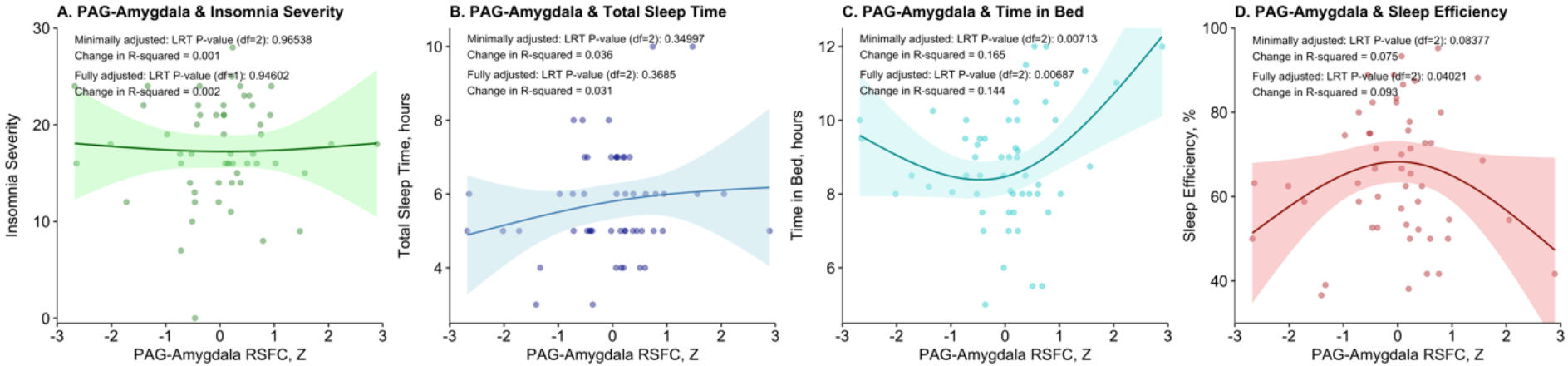


Figure 6-19. PAG-amygdala functional connectivity is associated with time in bed and sleep efficiency in fibromyalgia.

Relationships between PAG-amygdala resting state functional connectivity (RSFC) and insomnia severity (A), sleep duration (B), time in bed (C), and sleep efficiency (D) are displayed for fibromyalgia patients. Both lower and higher PAG-amygdala RSFC is associated with greater time in bed (C) and lower sleep efficiency (D). There was no significant association with insomnia severity (A) or sleep duration (B). RSFC measured during rs-fMRI during baseline visit, and modelled using second-order polynomial term to account for non-linear association. Insomnia severity measured with ISI. Sleep duration (total sleep time), time in bed, and sleep efficiency are self-reported and derived from the Pittsburgh Sleep Quality Index (PSQI). Minimally adjusted model includes age and sex. Fully adjusted model includes education (degree, no degree), employment status (employed, not employed), and analgesia use (opioids, tricyclic antidepressants, or gabapentinoids). Training blocks omitted. Regression slopes with 95% confidence intervals are shown. Likelihood ratio test (LRT) p-values and changes in R^2 are provided for the contribution of PAG-Amygdala RSFC in the models. RSFC, resting state functional connectivity; FM, fibromyalgia; ISI, insomnia severity index; LRT, likelihood ratio test; df, degrees of freedom.

6.3.6 Model diagnostics

Diagnostic plots showed no strong violations of linear regression assumptions. Residuals vs fitted plots indicated homoscedasticity, while QQ plots and histograms showed residuals were approximately normal, with minor deviations at the tails in some models for RT variability. VIF values were low (< 2) for all models, indicating no multicollinearity. Overall, model assumptions were adequately met (Supplementary Figure B-1 to Supplementary Figure B-8).

6.3.7 Objective 4: Derive a neuromarker of sustained attention in fibromyalgia and compare the network pattern to one derived from healthy adults.

6.3.7.1 Objective 4: FM-saCPM from resting state predicts sustained attention

The fibromyalgia-specific sustained attention connectome predictive model (FM-saCPM) was derived, identifying a high-attention network (1,149 edges, 3.2% of edges) and a low-attention network (439 edges, 1.3% of edges). Network strength, calculated as the sum of edge strengths, significantly predicted sustained attention accuracy (d') during the NVT. The high-attention network (**Table 6-2,** r=0.53, P=0.001) and low-attention network (**Table 6-2,** r=0.50, P=0.001) showed moderately strong correlations with d' (**Figure 6-20A&B**), and a combined general linear model yielded similar results (r=0.45, P=0.001, **Figure 6-20C & Supplementary Figure E-9**).

There was no relationship between the FM-saCPM and subjective cognitive difficulties (BC-CCI), although the high-attention network showed a trend toward significance (**Table 6-2,** r=0.2, P=0.0599). These findings align with prior results from the saCPM derived in healthy populations[379].

Network	d'	BC-CCI
High-attention	R=0.53 (P=0.001)	R=0.20 (P=0.0599)
Low-attention	R=0.50 (P=0.001)	R=0.15 (P=0.134)
GLM	R=0.45 (P=0.001)	R=0.12 (P=0.192)

Table 6-2. Correlations between FM-saCPM predictions and sustained attention (d') and subjective cognitive difficulties (BC-CCI).

The predictive networks from the FM-saCPM derived from training rs-fMRI data on d' correlated with observed d', but not BC-CCI scores. d', sensitivity on NVT. BC-CCI, British Columbia Cognitive Complaints Inventory. R, Pearson's correlation. GLM, general linear model combining high- and low-attention networks. Mean correlation coefficients from 1,000 iterations. P-values derived using 1,000 permutations.

6.3.7.2 Objective 4: Distinct functional anatomy of high- and low-attention networks in FM-saCPM

Both high- and low-attention networks involved edges across all RSNs. In the high-attention network, connections between subcortical, cerebellar, motor, and visual networks were associated with better sustained attention (**Figure 6-21A & Figure 6-22B**). Conversely, the low-attention network was dominated by connections between medial frontal, motor, and subcortical regions, associated with worse attention (**Figure 6-21B & Figure 6-22B**). Motor and visual networks featured more prominently in the high-attention network, while medial frontal and frontoparietal connections predominated in the low-attention network (**Figure 6-22C**).

6.3.7.3 Objective 4: Minimal overlap between FM-saCPM and saCPM models

Comparisons between the FM-saCPM and saCPM networks demonstrated minimal overlap in connectivity patterns associated with sustained attention. Only 59 edges overlapped in the high-attention networks (**Figure 6-23A**) and 16 in the low-attention networks (**Figure 6-23B**). The FM-saCPM high-attention network featured more connections involving motor

and subcortical-cerebellar networks and fewer from the frontoparietal network (**Figure 6-23C**). Similarly, the FM-saCPM low-attention network had greater involvement of medial frontal and subcortical-cerebellar networks, with fewer frontoparietal connections (**Figure 6-23D**).

6.3.7.4 Objective 4: The saCPM model is not associated with sustained attention or cognitive difficulties in fibromyalgia

When applied to rs-fMRI data from fibromyalgia patients, the saCPM model showed no significant association with sustained attention (**Figure 6-24A & Supplementary Figure E-10A**, d', rho=-0.05, P=0.62) or subjective cognitive difficulties (**Figure 6-24B & Supplementary Figure E-10B**, BC-CCI, rho=-0.19, P=0.94).

These findings underscore that CPM models for attention derived from fibromyalgia patients (FM-saCPM) are distinct from those developed in healthy adults (saCPM[379]).

In summary, this study identified two resting-state functional connectivity networks that are associated with sustained attention, but not subjective cognitive difficulties, in fibromyalgia patients. These networks are distinct from those found in healthy adults.

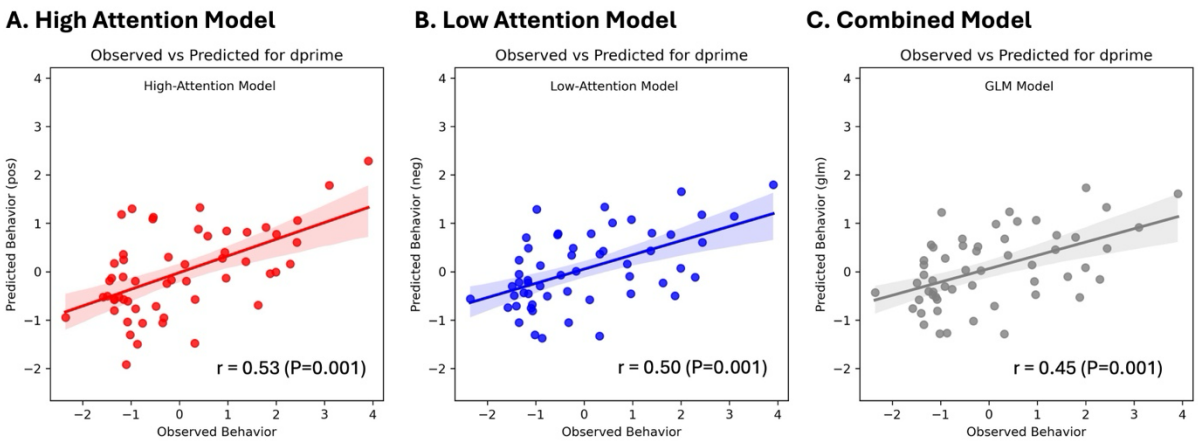


Figure 6-20. Connectome predictive models from rs-fMRI data associated with sustained attention (FM-saCPM model).

Scatter plots display correlation between observed NVT performance (d') and predicted performance by high-attention (A), low-attention (B) networks, and combined general linear models (GLM, C) which contain both high- and low-attention networks strength. The x-axis represents the observed de-meaned D' from the NVT for the high-attention (A), low-attention (B), and combined (GLM) model (C). The y-axis represents the predicted D' score from the CPM. The correlation between observed and predicted D' scores are shown. Higher values for D' indicate better attention. The CPM models were trained using k-fold cross-validation using 10 folds and 1,000 iterations. P-values obtained using 10,000 permutations. NVT, number vigilance task. D', sensitivity on NVT; a measure of task accuracy.

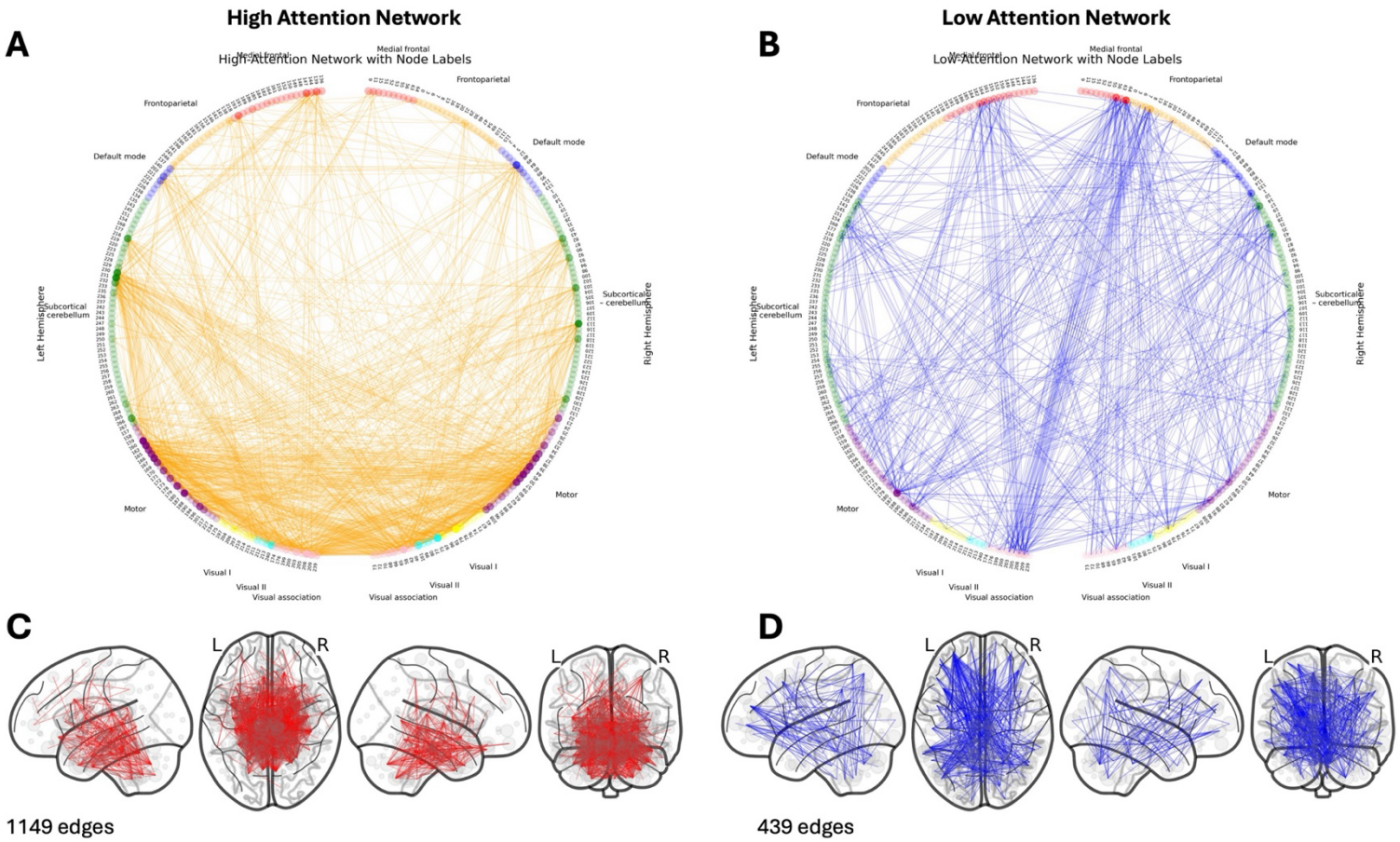


Figure 6-21. Functional connectomes (edges) for the high-attention (A) and low-attention (B) networks associated with sustained attention.

(A) The 1,149 edges in the high-attention network (i.e. predicting high d' in NVT) which appear in 95% of folds are visualised in orange. (B) The 439 edges in the low-attention network (i.e. predicting lower d' in NVT) are visualised in blue. Network nodes are grouped by hemisphere into canonical resting state networks. Networks were created with an edge-selection threshold of r>|0.3|. Edges which appear in 95% of folds are displayed. Node opacity corresponds to the number of connections from that node. Visualisation of functional connectomes (edges) for high-attention (C) and low-attention (D) networks on a brain map. Grey circles represent nodes. Node size corresponds to the number of edges. NVT, number vigilance task. L, left. R, right.

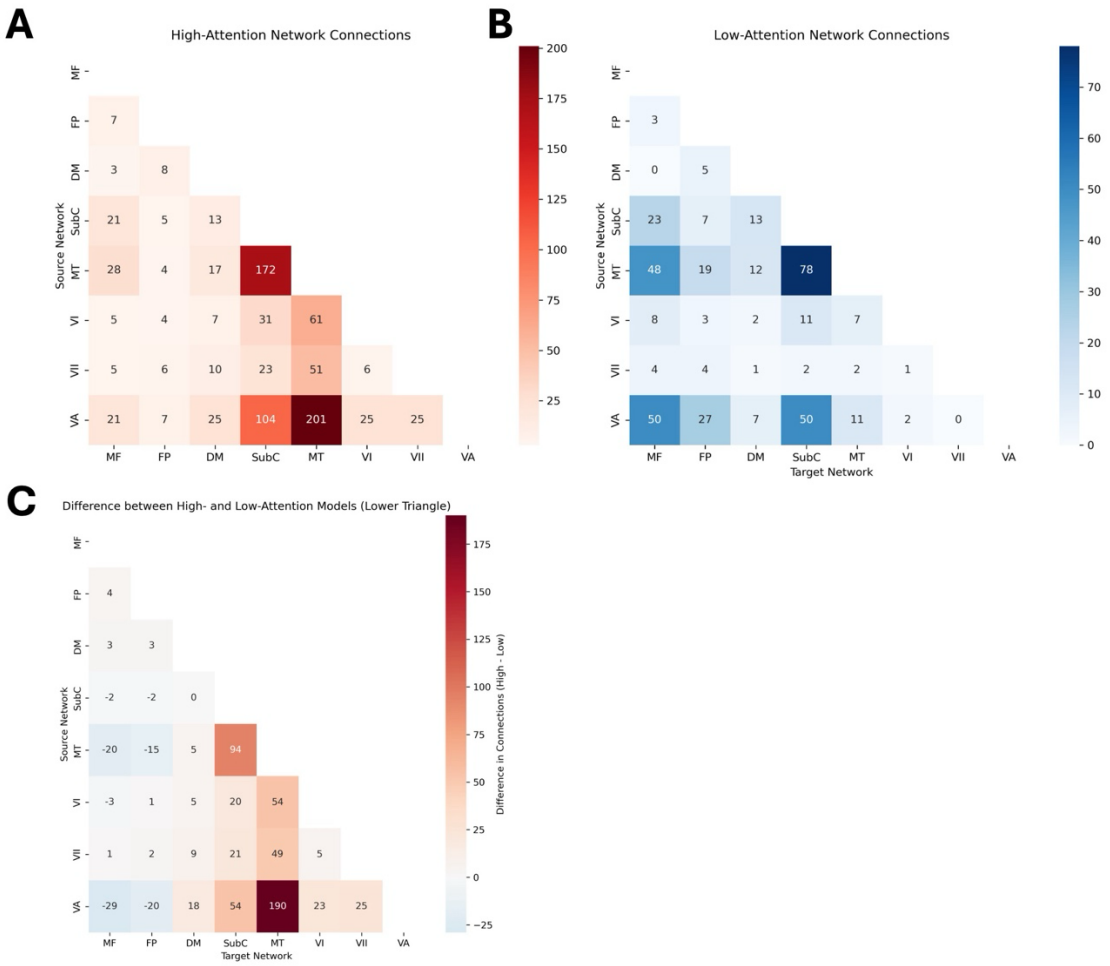


Figure 6-22. Resting state network distribution of edges in and between CPM models.

The number of edges between each RSN pair for the high-attention (A) and low-attention networks (B). The difference in the number of edges between each pair of RSNs was calculated by subtracting the number of edges in the low-attention network from the high-attention network (C). RSN, resting state network. MF, medial frontal. FP, frontoparietal. DM, default mode. SubC, subcortical. MT, motor. VI, visual I. VII, visual II. VA, visual association.

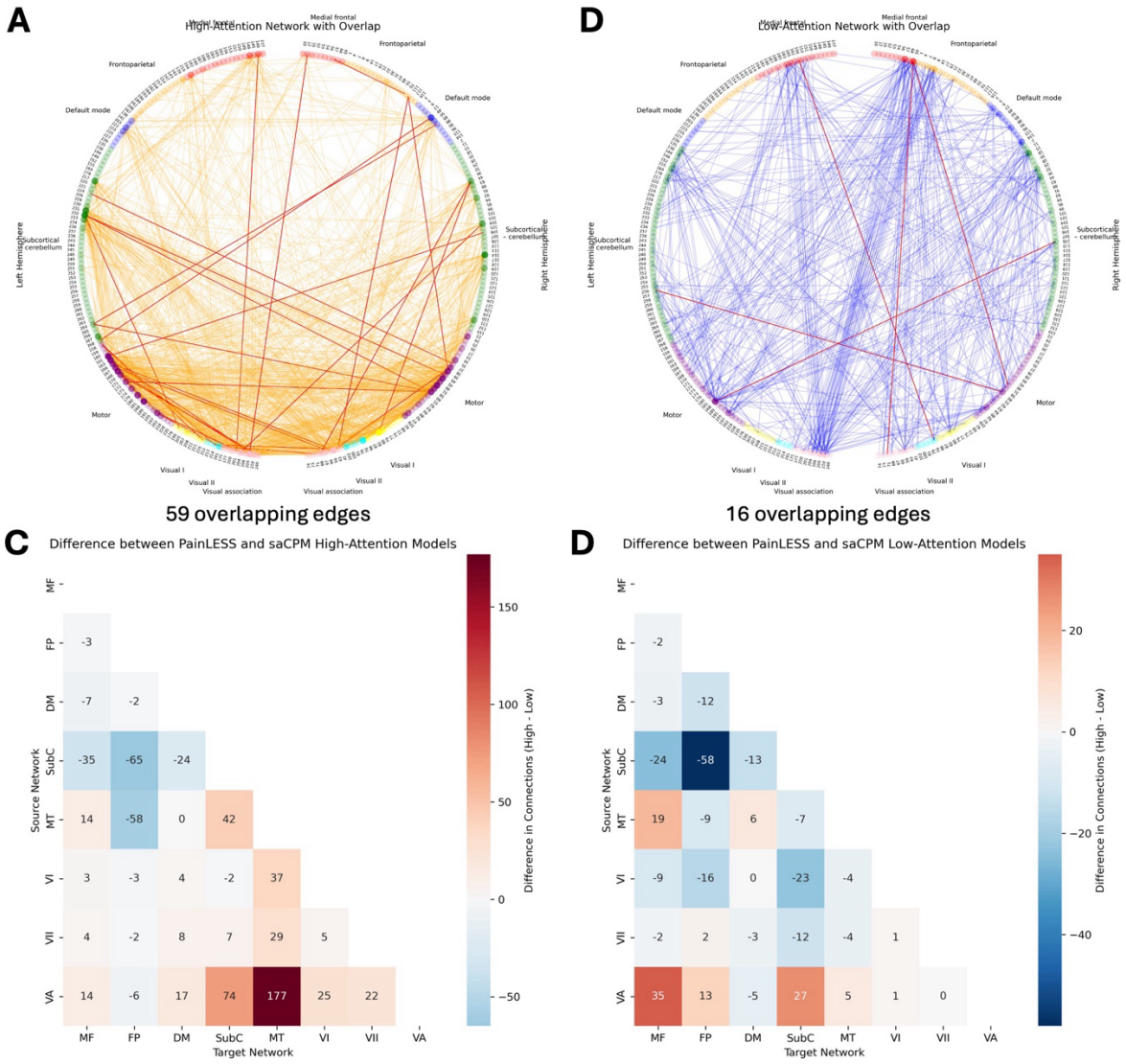


Figure 6-23. Minimal overlap between FM-saCPM and saCPM models

The overlap between edges in the high-attention (A) and low-attention (B) networks from the PainLESS study and edges which appear in the saCPM model (Rosenberg 2016) are highlighted in red. The difference in the number of edges between each pair of RSNs between the PainLESS CPM model and saCPM model was calculated by subtracting the number of edges in the low-attention network from the high-attention (C) and low-attention network (D).

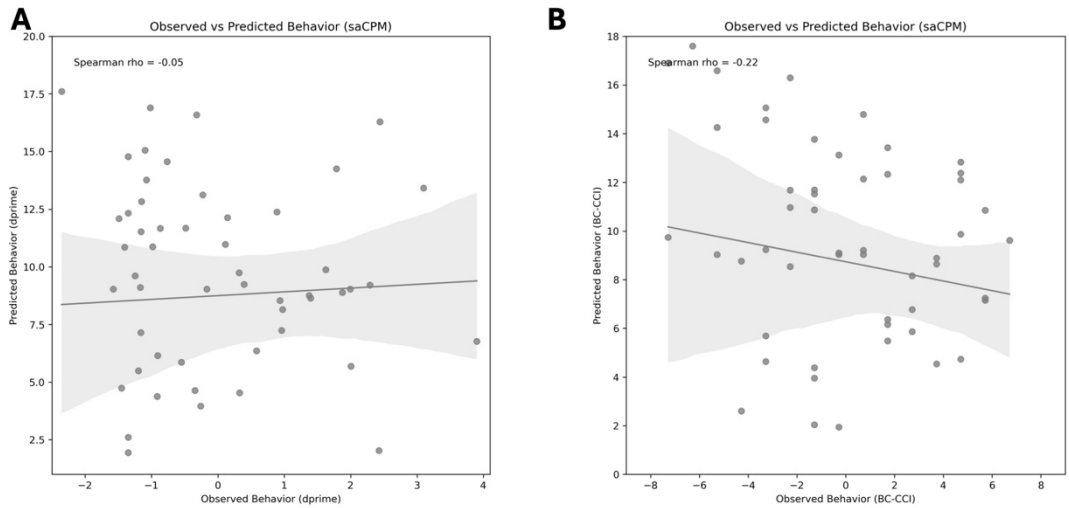


Figure 6-24. saCPM model is not associated with sustained attention or cognitive difficulties in fibromyalgia.

The saCPM defined by Rosenberg et al. (2016) does not predict sustained attention (A) in fibromyalgia patients. Although saCPM scores were negatively correlated with subjective cognitive difficulties (B), this relationship was not statistically significant. Higher values of D' indicate better sustained attention. Higher values of BC-CCI indicate more severe self-reported cognitive difficulties. D', task accuracy on Number Vigilance Task (NVT). BC-CCI, British Columbia Cognitive Complaints Inventory. Rho, Spearman's correlation. saCPM, sustained attention connectome predictive model (taken from Rosenberg et al., 2016).

6.4 Discussion

6.4.1 Summary

6.4.1.1 Fibromyalgia vs healthy controls

Patients with fibromyalgia demonstrated poorer sustained attention compared to healthy controls, as evidenced by worse accuracy (hit rate) and greater RT variability, indicative of impaired focus or "state instability". Higher RT variability was associated with reduced accuracy and increased false alarms (**Figure 6-4**). Notably, there was no speed-accuracy trade-off for correct responses in fibromyalgia; faster responses were associated with higher accuracy. However, fibromyalgia patients showed a trade-off for errors, with faster RTs correlating with increased false alarms, suggesting they needed to slow down to minimise mistakes, unlike healthy controls (**Figure 6-4D&E**).

Attentional focus in fibromyalgia participants was more sensitive to fatigue and motivation, with greater RT variability observed in those reporting higher fatigue and lower motivation levels (**Figure 6-6E & Figure 6-7E**). Despite these attentional deficits, both groups showed similar rates of performance decline over time, indicating that while fibromyalgia patients had a baseline disadvantage in focus and attention, their rate of deterioration was comparable to healthy controls (**Figure 6-3**).

These findings suggest that individuals with fibromyalgia face significant challenges in maintaining sustained attention compared to healthy controls, with their performance heavily influenced by fatigue and task demands. Interventions aimed at reducing fatigue and enhancing focus may help mitigate these difficulties.

6.4.1.2 Symptom severity in fibromyalgia

Fibromyalgia symptom severity (FIQR) was associated with impaired task performance, with the strongest effect observed with increased state instability, with a weaker association with accuracy, and no association with speed (RT) (**Figure 6-8**). Among individual symptoms, higher baseline pain intensity and lower baseline motivation were independently associated with increased RTV, suggesting that these factors impair focus during sustained attention tasks (**Figure 6-9A)**. These findings align with a "opportunity cost model" of performance, which posits that individuals with greater motivation are better able to maintain focus[143]. Interestingly, baseline fatigue did not independently contribute to state instability. The lack of covariance between pain and motivation at baseline implies that these factors exert independent influences on attentional performance **(Figure 6-9B**).

Sleep disturbance also emerged as a key factor, with both self-reported sleep quality (ISI) and abnormally short and long self-reported TST and time-in-bed associated with greater RTV and reduced accuracy in a U-shaped relationship (**Figure 6-13**). This relationship mirrors findings from UK Biobank (see Chapter 3, section 3.3.6.1), where similar quadratic associations were observed. The relationship was most marked for TST and time in bed, suggesting these factors may play a particularly important role in sustained attention. In contrast, brain-fog, depression, anxiety, and analgesia use were not associated with sustained attention performance, suggesting that these factors play a minor role in sustained attention in fibromyalgia.

Pain intensity partially mediated the relationship between overall symptom severity (measured by FIQR) and task accuracy. Furthermore, when examining pain characteristics, intensity and neuropathic symptoms – rather than widespread pain – were independently associated with impaired attention, again echoing the results described in Chapter 3 (see section 3.3.6.2).

A novel finding was the quadratic association between PAG-amygdala connectivity and sustained attention metrics: speed, state instability and accuracy (**Figure 6-16**). Both increased and decreased PAG-amygdala RSFC demonstrated a strong relationship with faster RTs and greater errors, suggesting its potentially involvement in the speed-accuracy trade-off observed in fibromyalgia. Recent imaging studies have shown that PAG functional connectivity plays a role in attentional modulation of pain[344; 345]. This warrants further investigation using task-based fMRI to explore the role of PAG-amygdala connectivity in attentional performance. Interestingly, PAG-amygdala RSFC also demonstrated a strong U-shaped association with time in bed and sleep efficiency, suggesting that the DPMS may play a role in the relationship between sleep and cognitive performance in fibromyalgia (**Figure 6-19**).

6.4.2 Sustained attention in fibromyalgia

Cognitive deficits, including impairments in attention and working memory, are well-documented in fibromyalgia[126; 127; 149; 167; 168; 313]. However, relatively few studies have specifically examined *sustained* attention. Research using the Attention Network Test-Interaction (ANT-I) found fibromyalgia patients demonstrated slower RT and more errors than healthy controls, though pain intensity was not associated with

these deficits[167; 313]. This may be because pain affects response *variability*, which was not assessed in these studies, rather than speed. However, Fang *et al.* identified pain intensity as a predictor of attentional lapses during a 3-minute psychomotor vigilance task (PVT), which was partially mediated by subjective sleep quality but not duration[149]. This aligns with the current findings, where pain intensity was associated with RT variability and accuracy but not RT itself, suggesting pain impacts attentional stability rather than response speed.

When compared to attention difficulties in long COVID patients who completed the same NVT, fibromyalgia patients demonstrated similarities, such as impaired task accuracy but preserved speed[519]. This suggests phenotypical similarities between sustained attention difficulties in fibromyalgia and long COVID.

6.4.3 State instability

The study of state instability in sustained attention highlights how performance fluctuates between periods of optimal focus ("in the zone") and lapses in attention ("out of the zone"). These fluctuations are not simply decrements over time but reflect dynamic shifts influenced by internal and external factors. RT variability is a hallmark indicator of such lapses[142]. Factors such as task motivation, mind-wandering, and external distractors like pain or sleep deprivation can affect these states, with variability indicating a struggle to maintain stable cognitive control[143; 384; 416].

In fibromyalgia, increased state instability may reflect heightened susceptibility to such factors. External influences, including pain intensity, and internal elements, like

motivation deficits, may compete for cognitive resources, undermining sustained attention. These findings align with frameworks that emphasise the interplay of cognitive control and arousal in managing attentional stability[384].

6.4.4 Pain and sustained attention

Pain may divert cognitive resources away from sustained attention leading to increased state instability reflected in increased RT variability and worse accuracy, as seen in fibromyalgia patients. The findings align with studies demonstrating pain intensity's association with worsened sustained attention, especially when pain is assessed contemporaneously with cognitive tasks[127]. However, when pain is measured at a temporal distance from the task, its impact on attention appears diminished[126; 167]. Neuropathic pain, similarly, has been shown to impair sustained attention, further highlighting the cognitive burdens imposed by pain conditions[215]. This suggests that the timing and nature of pain assessment are important for understanding its cognitive implications.

6.4.5 Sleep quality and sustained attention

In contrast to pain, where there is a relative paucity of literature, there is consistent evidence that sleep is important for sustained attention. Acute sleep deprivation increases RT variability, slows responses, and raises error rates in sustained attention tasks, as observed in studies employing tasks similar to the NVT, such as the PVT[226] and ANT-I[290]. Sleep deprivation particularly affects visual attention, likely due to susceptibility of eye opening to sleep pressure during tasks requiring sustained focus[128]. Indeed, sleep deprivation appears to have more pronounced effects on

sustained attention than other cognitive domains such as working memory[130; 132]. These findings align with my observations linking abnormal sleep duration in fibromyalgia, in particular, with greater state instability and attentional lapses.

At the population level, both short and long sleep durations show U-shaped relationships with cognitive performance and decline[281; 442; 496; 510]. Furthermore, subjective sleep quality is also associated with attentional impairments, as demonstrated in prior work[177]. Short sleep may exacerbate cognitive impairments via insufficient sleep consolidation processes and insufficient restorative sleep, often linked to insomnia or lifestyle factors such as shift-work or caring responsibilities. While long sleep is tied to disrupted sleep architecture associated with fragmented or non-restorative sleep, perhaps due to conditions like sleep disordered breathing or periodic limb movements[33]. Although I excluded sleep apnoea and restless legs syndrome from this study, sleep may still be disturbed by pain in fibromyalgia, and thus long sleep may not be as restorative as “normal” sleep in this group. Furthermore, self-reported sleep may be vulnerable to reverse causation. People with insomnia may under-report sleep, while those with fragmented sleep may over-report sleep[133].

6.4.6 Potential mechanisms

Multiple mechanisms may explain the observed associations between sleep disturbance and sustained attention in fibromyalgia. Neuroinflammation may play a role in the cognitive impairments seen in various conditions, such as fibromyalgia and long COVID[272; 276]. However, studies directly linking inflammation with cognitive performance in fibromyalgia are lacking.

The glymphatic system, active predominantly during slow-wave sleep (SWS), plays a critical role in clearing metabolic waste from the brain[87]. Disruption of this system due to poor sleep may exacerbate neurodegenerative processes and cognitive decline, as seen in conditions like Alzheimer's disease[87]. Structural changes in grey and white matter associated with both short and long sleep durations have also been implicated in executive dysfunction, although specific deficits in sustained attention linked to such changes remain understudied[442]. For instance, state instability during attention tasks has been correlated with increased activity in the DMN and decreased activation of the DAN, highlighting potential neural mechanisms[142], but these changes have not been examined in relation to sleep.

6.4.7 Mood and subjective cognition and sustained attention

6.4.7.1 Brain-fog

Few studies have examined the relationship between brain-fog and sustained attention in chronic pain or in insomnia. In a recent trial of insomnia patients, digital CBT-I (*Sleepio*) improved subjective but not objective cognition, although sustained attention was not one of the domains evaluated[253]. Evidence from post-COVID studies highlights that subjective cognitive complaints, such as brain-fog, are not associated with objective measures of sustained attention[122]. These discrepancies are consistent with findings in aging populations, where subjective memory complaints often weakly correlate with objective performance[8; 423]. In the current study, brain-fog was not significantly associated with sustained attention, perhaps because brain-fog more strongly correlates with domains like memory rather than attentional processes[225]. This aligns with broader literature indicating that subjective cognition

is influenced by factors like fatigue and depression, which are distinct from those affecting attentional performance[70].

6.4.7.2 Anxiety and depression

Anxiety and depression have complex relationships with cognition. While anxiety was modestly associated with executive functions in large cohorts like the UK Biobank (see Chapter 3, section 3.3.6.1), its association on sustained attention appears minimal in this study, echoing work in long COVID[519]. Similarly, depression was not meaningfully associated with sustained attention in this study. These findings suggest that mood may have a limited role in sustained attention deficits compared to other domains of cognition, such as memory or executive functioning.

6.4.8 DPMS, sleep & sustained attention

This study identified a strong association between PAG-amygdala connectivity and sustained attention performance, as well as sleep parameters, but not pain intensity. Evidence from animal studies support a potential the role of the DPMS, including the PAG and amygdala, in mediating the effects of sleep deprivation on nociception and potentially cognition. Acute sleep deprivation in rats reduces GABAergic activity in the PAG, reducing descending inhibitory control over pain[449]. In another animal study, chronic sleep deprivation, on the other hand, increases PAG activity and nociceptive responses, which can be reversed by lesioning the PAG[398]. Similarly, acute sleep deprivation enhanced nociceptive response to a surgical stimulus in rats, which was mediated by increased pain facilitation activity in the RVM[508]. This suggests that sleep deprivation disrupts balance between pain inhibition and facilitation in the DPMS. Moreover, GABAergic neurons in the ventrolateral PAG have been shown to regulate

REM and NREM sleep transitions, highlighting the region's dual role in sleep and pain modulation[486].

The amygdala's role in sleep disturbances is well-documented. Insomnia is associated with altered amygdala connectivity, including increased connections to motor-related regions and decreased connectivity with emotion-regulation areas such as the insula and thalamus[209]. Similarly, short sleep duration has been linked to reduced amygdala-ventromedial PFC connectivity, indicating impaired emotional regulation[237]. Although these studies did not directly examine the PAG or DPMS activity, they suggest that disrupted sleep may influence broader neural networks, including those involved in pain perception and sustained attention.

6.4.9 Comparison to UK Biobank results in Chapter 3

The findings from UK Biobank (Chapter 3) and this chapter reveal both similarities and differences in how fibromyalgia symptom severity relates to cognitive performance. In both studies, pain intensity and abnormal sleep duration were associated with cognitive impairments, with a strong relationship observed for sleep duration in particular; while depression, brain-fog, and analgesic use were not. Of interest, neuropathic pain severity was also associated with cognition in both studies. This emphasises the central role of pain and sleep in cognitive performance across cohorts. Anxiety mediated executive function in UK Biobank but did not impact sustained attention in this study, suggesting anxiety may affect other cognitive domains besides executive function[126; 127]. Baseline fatigue, measured using a visual analogue scale (VAS) just prior to the task in the PainLESS cohort, was a significant predictor of attention, in contrast to UK Biobank, where the Fatigue Severity Scale (FSS), which was

not assessed just prior to the cognitive tasks, did not mediate effects. Although the FSS and VAS measures have been shown to be highly correlated[460], the timing of assessments in relation to cognition may explain the divergent findings. The PainLESS study measured sustained attention, which is a critical aspect of daily functioning and less abstract than executive function measures like latent factor for EF used in UK Biobank.

6.4.10 CPM: summary of findings

The current study utilised Connectome Predictive Modelling (CPM) to identify two networks—high-attention and low-attention, with strength in the high-attention network demonstrated a strong positive correlation with sustained attention in fibromyalgia, while strength in the low-attention network correlated negatively (**Figure 6-20**).

6.4.10.1 Comparison to existing models.

The identified fibromyalgia-specific CPM did not significantly overlap with the saCPM derived from healthy adults and replicated in ADHD[379] (**Figure 6-23**). This divergence suggests that neural mechanisms of attention deficits in fibromyalgia may be distinct from those seen in adults without chronic pain, or in ADHD. These attentional deficits may be shaped by factors more specific to fibromyalgia and other chronic pain conditions, such as pain intensity and sleep disturbances. Pain intensity, in particular, may contribute to diversion of attentional resources, exacerbating the difficulty of sustained attention tasks in fibromyalgia patients. These factors were observed to be strongly associated with poor sustained attention in this study. This echoes a study where chronic pain patients displayed similar performance on a N-Back test, but recruited different network patterns, compared to healthy controls[476].

However, the observed differences may also be due to methodological differences, foremost the different sustained attention tasks employed to develop each model. The NVT used in the current study involves nine 60-second blocks, where non-target ("no-go") stimuli outnumber target ("go") stimuli. In the gradCPT task, meanwhile, used to derive the saCPM, target stimuli outnumbered non-target stimuli[378]. Another key difference was that the gradCPT task was not broken up into blocks with self-rated assessments of subjective feelings, unlike the NVT. These blocks may potentially act as 'rest periods' affecting the level of vigilance decrement observed.

6.4.10.2 Ranking neural regions

CPM outputs can be utilised to rank brain regions for future targeting using several methods. The most straightforward approach is to examine node degree within the predictive network, i.e. counting how many predictive edges involve each node or region. A higher degree suggests that the region serves as a connectivity hub and may play an important role in the phenotype of interest. For example, Yang *et al.* reported that consensus edges (those appearing in all iterations) were grouped by macroscale brain regions, showing that the prefrontal cortex, insula, and subcortical regions were heavily involved in predicting opioid craving outcomes[511].

A related approach is to calculate node strength, defined as the sum of predictive edge weights (e.g., correlation coefficients or regression coefficients) connected to each node. This weighted measure reflects both the number and magnitude of a region's involvement in the model. For example, Spisák *et al.* found that nearly half of their

resting pain network model's predictive variance was explained by four strong connections, implicating key regions such as the posterior putamen, frontal pole, anterior cerebellum, and precentral gyrus[429].

Graph-theory centrality measures such as betweenness or eigenvector centrality can also be applied to the subgraph of predictive edges. These metrics help identify structurally influential nodes within the predictive network. For example, a node with high betweenness centrality lies on many shortest paths between other nodes, acting as a bridge between distinct network components[480]. Although not explicitly applied in the studies reviewed here, such approaches are supported in the CPM literature (e.g., Shen et al., 2017[409]) as a way to refine region selection based on network topology.

In addition to node-specific metrics, predictive edges or nodes can be grouped according to known anatomical or functional systems to assess broader patterns. For example, Yang *et al.* showed that edges within and between the frontoparietal network (FPN), sensorimotor network (SMN), and default mode network (DMN) were predictive of opioid craving levels, highlighting these systems as potential targets for intervention in opioid use disorder[511]. Similarly, predictive edges can be tallied within anatomical areas such as the prefrontal cortex to identify regions of interest based on their broader involvement.

In summary, CPM-derived data can inform the ranking of brain regions using node degree, node strength, network centrality, and anatomical or functional groupings. While CPM typically identifies distributed, whole-brain networks, these metrics allow for the prioritisation of regions most consistently and strongly implicated in predictive

models. Nonetheless, given the distributed nature of CPM outputs, it is often more appropriate to highlight sets of key regions rather than a single dominant target.

6.4.10.3 Neural mechanisms

The high-attention network in fibromyalgia predominantly featured connections involving subcortical, cerebellar, motor, and visual attention networks. These networks have been implicated in bottom-up processes like arousal and target-driven attention[89; 456]. In contrast, the low-attention network was dominated by the medial frontal, frontoparietal and default mode networks, commonly associated with top-down control and default mode activity[103]. These patterns align with prior evidence suggesting that sustained attention relies on dynamic interplay between bottom-up arousal mechanisms and top-down task engagement[257].

6.4.10.4 Implications for sustained attention in fibromyalgia

The dissimilarity between the FM-saCPM and the saCPM underscores the importance of tailoring predictive models to clinical populations rather than extrapolating from models derived from healthy adults. The lack of generalisability of the saCPM to fibromyalgia suggests that cognitive impairments in chronic pain may not merely be an extension of typical attentional processes but involve distinct disruptions. The functional anatomy of the FM-saCPM highlights potential targets for interventions. Enhanced connectivity in motor and visual attention networks may be leveraged to improve attentional control in fibromyalgia. For example, interventions like

neurofeedback or transcranial magnetic stimulation targeting regions in these networks may enhance task performance and mitigate brain-fog.

While the identified networks correlated with sustained attention, they were not associated with self-reported brain-fog severity. This disparity suggests that subjective complaints in fibromyalgia may reflect broader affective or motivational disturbances rather than direct deficits in sustained attention. Prior research has similarly noted that subjective cognitive complaints in fibromyalgia are more closely related to fatigue, mood, and pain than to objective measures of cognition[247].

Furthermore, the non-linear relationship between PAG-amygdala connectivity and sustained attention identified in this study underscores the complexity of brain-pain interactions. Patients with both high and low connectivity exhibited poorer focus, suggesting a U-shaped association where deviations from optimal DPMS connectivity appear to be associated with impaired attentional control. This pattern mirrors findings in Chapter 3, where dysregulation of the DPMS impacts cognitive performance.

6.4.11 Strengths & limitations

This study examined sustained attention in a well-characterised cohort of fibromyalgia patients, with comparisons made to healthy controls. Sustained attention, a critical domain of cognition relevant to daily functioning, was evaluated using the NVT, a robust measure that has been studied in COVID, a condition which displays phenotypically similar cognitive symptoms. By incorporating detailed assessments of fibromyalgia symptom severity—such as pain, fatigue, motivation, and subjective sleep quality—my study offers a comprehensive exploration of the relationship between fibromyalgia

symptoms and cognitive performance. Additionally, the inclusion of neuroimaging provides valuable mechanistic insights into the neural basis of attention and sleep disturbances in fibromyalgia. The study controlled for important confounders, including socio-demographic variables and analgesic use.

Another strength of this study is its use of CPM to derive clinically relevant neural markers of sustained attention in fibromyalgia. The use of rs-fMRI data also facilitates application in chronic pain populations unable to tolerate prolonged task-based imaging. Nevertheless, validation of the neuromarker with task fMRI imaging would be beneficial to investigate the robustness of the model. Furthermore, the study is limited by a lack of replication of the neuromarker in another healthy and chronic pain populations. Additionally, the use of a single task (NVT) may limit generalisability, as attention deficits in fibromyalgia could vary across cognitive domains. Future work should replicate these findings using diverse cognitive paradigms and longitudinal designs to establish the temporal dynamics of CPM markers.

There are important limitations, however. The cross-sectional design precludes the ability to infer causality between fibromyalgia symptoms and sustained attention deficits, a limitation that will be addressed by the planned PainLESS trial (see 6.4.12.1). Cognitive testing was limited to sustained attention, without evaluation of broader cognitive domains such as memory and executive function. Selection bias is an important limitation, given differences in recruitment methods and limited demographic data on the healthy control group, which included age discrepancies and incomplete socio-demographic profiles. Furthermore, pain in fibromyalgia patients may

have affected motor responses during the NVT, potentially confounding the observed deficits in task performance.

The reliance on subjective sleep assessments, such as self-reported TST, is another limitation, as these measures are susceptible to recall bias compared to objective methods like actigraphy or PSG. Furthermore, the absence of data on chronotype, nap patterns, or recent caffeine intake further constrains the interpretation of sleep-related findings. However, all testing took place between mid-morning and mid-afternoon, so the effect of extreme times is limited. The relatively small sample size precluded a comprehensive simultaneous analysis of all SPACE (Sleep, Pain, Affect, Cognitive, Energy) factors and limited exploration of sex differences due to the predominantly female fibromyalgia cohort.

6.4.12 Conclusion and future work

6.4.12.1 Future work

Future research will expand upon these findings by exploring the impact of *Sleepio* (dCBTi) on sustained attention in fibromyalgia as part of the ongoing PainLESS trial. This will provide valuable insights into whether improving sleep quality translates to enhancements in cognitive performance. Additionally, given similar phenotypes, comparisons between fibromyalgia and long COVID are warranted to elucidate shared mechanisms underlying sustained attention deficits.

The CPM findings suggest avenues for further research, acting as a starting point to examine neural markers of sustained attention in chronic pain. In the PainLESS study, planned work includes examining whether dCBT-I induces connectivity changes in the

identified high- and low-attention networks. Future studies should evaluate the FM-saCPM in both healthy and broader chronic pain cohorts to determine its specificity to fibromyalgia. Further work should examine whether models derived from task fMRI experiments yield stronger predictive accuracy than rs-fMRI, particularly for capturing transient cognitive states during attention tasks. Studies incorporating multi-modal imaging (e.g., diffusion tensor imaging) would be helpful to elucidate structural correlates of the identified networks.

6.4.12.2 Conclusion

This study demonstrates that fibromyalgia patients exhibit worse accuracy and focus compared to healthy controls, while maintaining similar response speeds. These sustained attention deficits were closely associated with pain intensity, motivation (perhaps reflecting reward-responsiveness), and abnormal sleep durations. Notably, these cognitive impairments were not related to subjective cognitive complaints, mood disturbances, or medication use.

Altered DPMS function, as indicated by PAG-amygdala connectivity patterns, may underpin these associations, but further research, including task-based neuroimaging, is needed to confirm this hypothesis. Ultimately, integrating CPM with biomarkers of pain and fatigue may yield a better framework for understanding and mitigating cognitive impairments in fibromyalgia.

7 Chapter Seven: General discussion

7.1 Summary of main findings

In this thesis, I examined the relationship between nociplastic pain, exemplified by fibromyalgia, and cognitive impairment, focusing on the interplay between sleep, pain, and cognition.

Chapter 2 identified CBT-I as a promising intervention to improve sleep in fibromyalgia, while highlighting the need for scalable digital delivery methods.

In **Chapter 3**, I demonstrated that greater nociplastic pain severity is associated with worse executive function but does not accelerate cognitive decline over time. Pain severity, anxiety, and abnormal sleep duration partially mediate this cross-sectional association, suggesting that targeting sleep and pain could mitigate executive dysfunction in nociplastic pain.

Building on this, **Chapter 4** demonstrated altered DPMS connectivity is associated with nociplastic pain severity at a population-level, and implicated PAG-amygdala connectivity, in particular, as a potential mechanistic pathway linking nociplastic pain to executive dysfunction.

In the PainLESS study (**Chapter 5**), I established the feasibility of a digital CBT-I trial (*Sleepio*) in fibromyalgia, paving the way for a trial to evaluate its effects on quality of life and cognition.

Finally, in **Chapter 6** I demonstrated that fibromyalgia patients in the PainLESS study exhibited sustained attention deficits linked to pain intensity and abnormal sleep, aligning with my findings from the UK Biobank in **Chapter 3**.

In summary, this thesis demonstrates that nociplastic pain is associated with significant cognitive impairments, particularly in executive function and sustained attention, largely mediated by pain severity and sleep disturbances. Digital CBT-I is a promising intervention with potential to improve both cognition and quality of life in fibromyalgia.

7.2 Nociplastic pain is associated with worse executive function

In this thesis I demonstrate a robust cross-sectional relationship between nociplastic pain, particularly fibromyalgia, and cognitive impairment, focusing on executive function and sustained attention. Pain severity and sleep disturbances emerged as the factors most strongly associated with these cognitive deficits, while other factors like anxiety, fatigue, and medication use had more nuanced or context-dependent effects. These findings establish a foundation for understanding cognitive dysfunction in fibromyalgia and inform potential therapeutic approaches.

At a population level, chronic pain was associated with a 3.5 centile lower executive function, and among adults with chronic pain, greater nociplastic pain severity was associated with worse cognitive performance. This severity did not accelerate cognitive decline over time, offering reassurance about the long-term cognitive trajectory in nociplastic pain. In the PainLESS study, fibromyalgia patients exhibited impaired sustained attention, with lower accuracy and greater reaction time variability compared to healthy controls, reflecting difficulties in maintaining focus during cognitively demanding tasks.

Pain severity mediated cognitive impairment in both studies, suggesting it may exert a distracting effect on cognitive resources. Sleep disturbance, particularly short and long

self-reported sleep durations, also mediated these associations, highlighting the intertwined roles of pain and sleep in fibromyalgia-related cognitive impairments. Interestingly, neuropathic pain symptoms, but not widespread pain, were more strongly associated with cognitive deficits, challenging prior assumptions about the role of pain distribution. This may reflect the uniquely distracting features of neuropathic pain, the important role of centralised pain, or the ability of instruments like DN4 and PainDETECT to capture nociplastic pain characteristics[202; 366; 369]. However, the potential role of pain interference—a critical aspect of the cognitive-pain relationship—remains unexplored in this work, representing an important avenue for future research[514].

Discrepancies between findings from UK Biobank and the PainLESS study underline the complexity of these relationships. For example, fatigue was associated with sustained attention deficits in PainLESS but not executive dysfunction in UK Biobank, possibly due to differences in timing and scope of fatigue assessments.

The role of affective symptoms was nuanced. Anxiety was associated with executive function at a population level but not with sustained attention in PainLESS, possibly due to the smaller sample size or differences in the cognitive domains assessed. Depression, on the other hand, was not linked to worse cognitive performance in either study and, in UK Biobank, was associated with better outcomes after adjusting for other SPACE symptoms. This is in contrast to much of the existing literature, where depression has been linked to executive dysfunction in its own right[302; 465], and in the context of chronic pain[79].

Analgesia use, including opioids, tricyclic antidepressants and gabapentinoids, was not linked to cognitive impairment. However, this finding must be interpreted cautiously

due to several limitations, including measurement error due its self-reported nature, potential confounding by indication, the low prevalence of analgesic use in UK Biobank, and the lack of data on dose and duration of therapy. Although self-reported prescription data is susceptible to under-reporting[487], self-reported *current* analgesia use in chronic pain patients appears to be largely accurate[255]. The observed absence of association could be explained by the competing effects exerted by analgesia on cognition; they may benefit cognition by alleviating pain while potentially introducing cognitive side effects, resulting in a net neutral relationship[351].

Notably, self-reported cognitive complaints were not associated with objective cognitive performance in either study. This disconnect could stem from differences in measurement tools, cognitive domains, and populations. Instruments like the cognition item of the SSS and BC-CCI may lack sensitivity to detect self-reported cognitive complaints in FM[137]. Additionally, prior research has focused on memory, which may align more closely with self-reported cognitive complaints[68], while in this thesis I focused on executive function and sustained attention. In chronic pain, interoceptive disturbances may further contribute to the mismatch between subjective and objective cognition[56]. Finally, self-reported cognitive complaints and objective cognitive deficits may represent distinct phenomena: the former reflecting broader affective or motivational disturbances and the latter driven primarily by pain and sleep disruption[68].

In summary, the findings highlight the complex interplay between nociplastic pain, sleep, and cognition. Pain severity and sleep disturbances consistently emerged as key contributors to cognitive impairments in both studies, while the roles of affective

symptoms, medication use, and self-reported cognitive complaints remain areas for further exploration.

7.3 There is altered DPMS connectivity in nociplastic pain

The findings from this thesis reinforce the use of the fibromyalgia index (FMI) as a reliable measure of nociplastic pain severity, as it was associated with behavioural characteristics associated with nociplastic pain, as well as strength of both functional and structural connectivity within the DPMS at a population level. Notably, the association was relatively stronger with structural connectivity, suggesting that these changes may reflect long-standing, pain-induced neural adaptations rather than transient functional alterations. However, the cross-sectional nature of these studies limits the ability to infer causality.

PAG-amygdala connectivity emerged as a key mediator between symptom severity and executive dysfunction, linking pain with cognitive impairments. This pathway appears to play an important role in linking pain with cognitive impairments. In PainLESS, PAG-amygdala connectivity was not only associated with cognitive performance but also with sleep characteristics, including sleep efficiency and time in bed. These results suggest a multifaceted role for this pathway, extending beyond its established involvement in pain modulation (via the PAG) and affect regulation (via the amygdala). Further support comes from animal studies demonstrating that poor sleep modulates PAG activity, potentially impairing both pain modulation and cognitive function[486]. The interplay between sleep, pain, and cognition warrants further study, particularly the bidirectional effects of sleep disturbances on DPMS function. The PainLESS study offers an opportunity to test whether dCBT-I can improve PAG-amygdala connectivity,

with potential downstream effects on sleep, cognitive performance, and pain outcomes. This research could inform the development of more targeted interventions for nociplastic pain.

7.4 CBT-I is a promising intervention to improve sleep and cognition in fibromyalgia

The association between sleep quality and cognitive impairment highlights sleep as a promising therapeutic target to alleviate cognitive dysfunction in fibromyalgia. Despite this potential, there is a paucity of studies evaluating cognition—whether subjective or objective—as an outcome in fibromyalgia[144; 317; 477]. Addressing this gap could provide valuable insights into the impact of sleep-focused therapies on cognitive performance and quality of life in fibromyalgia.

In Chapter 2, I identified CBT-I as a promising intervention to improve sleep in fibromyalgia. Although pharmacological options such as pregabalin may also hold potential for improving sleep, its use requires careful consideration of abuse potential. Face-to-face CBT-I, though effective, faces scalability challenges in fibromyalgia, where accessibility and physical limitations may hinder attendance. Digital CBT-I has shown promise in addressing these barriers in other conditions, demonstrating effectiveness in insomnia[141], including improvements in subjective cognition[253]. Given these findings, a RCT of dCBT-I in fibromyalgia is the logical next step. My feasibility trial demonstrates that a RCT of dCBT-I is a viable in fibromyalgia, with recruitment, engagement, and follow-up rates that were largely acceptable. These results provide a strong foundation for the ongoing trial, which aims to evaluate the impact of dCBT-I on quality of life in fibromyalgia. This larger trial, funded and currently

underway, is expected to be completed by Spring 2025. The results of this trial will provide important evidence for the role of dCBT-I in addressing both sleep disturbances and their downstream effects on cognition and quality of life in fibromyalgia. If successful, dCBT-I could represent a scalable, non-invasive intervention to mitigate the multifaceted challenges faced by individuals with fibromyalgia, offering a significant step forward in the management of this condition.

7.5 Connectivity patterns of sustained attention in fibromyalgia are different to healthy adults

Connectivity patterns associated with sustained attention in fibromyalgia differ markedly from those observed in healthy adults, with minimal overlap between the fibromyalgia-specific connectivity model and an established model derived from pain-free individuals[379]. This suggests that the neural mechanisms underpinning sustained attention deficits in fibromyalgia may be distinct, perhaps shaped by the chronic pain, sleep disturbances or other symptomatology characteristic of this condition.

These differences highlight the need to tailor models of cognitive function to clinical populations rather than extrapolating from healthy adults. Such tailored models could provide more accurate neuromarkers for assessing cognitive impairment in fibromyalgia and guide the development of targeted interventions.

Future work will evaluate whether the fibromyalgia-derived model aligns with connectivity patterns observed during evoked tonic pain in healthy adults. This comparison is essential to determine whether the disruptions in sustained attention seen in fibromyalgia are fundamentally different from those elicited by acute pain in

pain-free individuals. If minimal overlap is observed, it would suggest that chronic pain creates unique neural adaptations affecting attention, distinct from transient pain states.

These findings underscore the interconnected role of pain and sleep disturbances in shaping cognitive processes in fibromyalgia. Identifying fibromyalgia-specific connectivity patterns could support the development of cognitive training or neuromodulation interventions tailored to the neural disruptions characteristic of this population.

7.6 Why is nociplastic pain not associated with an increased rate of cognitive decline?

Unlike prior studies that have linked chronic pain to accelerated cognitive decline (see **Table 1-1**), my findings did not demonstrate an association between nociplastic pain severity and a faster rate of decline in UK Biobank. Several factors, including methodological differences, the specific outcomes assessed, and characteristics of the study population, may explain this discrepancy.

7.6.1 Methodological considerations

While a small association between nociplastic pain severity and cognitive decline was initially observed, this effect was not present after adjusting for important confounders including educational attainment and social deprivation. In addition, I accounted for the non-linear effects of age on cognition, a factor often overlooked in similar studies, thereby minimising residual confounding related to age. The relatively short follow-up duration of approximately three years may have also limited the ability to detect

significant cognitive decline, especially given the gradual trajectory of changes in cognitive function over time. The cognitive tasks in UK Biobank, while practical for a large-scale study, may lack the complexity to capture subtle changes in cognition, potentially underestimating the relationship between pain and executive function over time[241].

A unique strength of this analysis lies in its examination of longitudinal factorial invariance. By ensuring that the cognitive measures remained stable and consistent over time, this approach provides confidence that observed changes reflect genuine differences in the underlying construct rather than shifts in the measurement properties themselves[495]. This is crucial in cognitive research, where evolving test characteristics or participant familiarity with tasks over time can confound interpretations of cognitive decline[493]. By addressing these methodological challenges, this study contributes to a more nuanced understanding of the relationship between pain and cognition and highlights the importance of rigorous measurement approaches in longitudinal research.

7.6.2 Differences in exposure and outcome measures

My study focused on nociplastic pain severity, whereas prior investigations examined pain interference, persistence, or other pain dimensions. These differing exposures may reflect distinct pathways linking pain and cognition. For instance, pain interference—capturing the extent to which pain disrupts daily life—may have more immediate and pronounced effects on cognitive outcomes than pain severity alone[147]. Moreover, memory, which tends to decline more quickly with aging[241],

has been the focus of previous studies that reported stronger associations with cognitive decline in pain populations[492].

7.6.3 Population differences

The UK Biobank population, comprising relatively healthy, well-educated, middle-aged individuals, may also contribute to the divergent findings[441]. This cohort's resilience to pain-related cognitive decline contrasts with older populations previously studied, who may be more vulnerable to systemic effects of pain and age-related cognitive decline[36; 203; 308; 385].

7.6.4 Reverse causation

Reverse causation, where cognitive function influences pain reporting, may also explain the findings. For example, individuals with better executive function may underreport pain or manage its impact more effectively, thus attenuating the observed association between pain and cognitive decline. Supporting this, evidence suggests that individuals with cognitive impairments, such as Alzheimer's disease or mixed dementia, report less pain compared to those with mild cognitive impairment or subjective cognitive impairment, potentially due to reduced recognition or communication of pain[52]. This underscores the complexity of disentangling pain and cognition in observational studies.

7.6.5 Future directions

While my findings suggest that nociplastic pain severity is not linked to accelerated executive function decline in the short term, they highlight the need for future research examining broader cognitive domains, including memory and dementia risk, over longer

follow-up periods. Investigating the role of pain interference, as opposed to pain intensity, may provide additional insights. Future studies should also explore whether different pain phenotypes, such as neuropathic pain, exert distinct effects on cognitive trajectories. Investigating whether addressing nociplastic pain and its symptoms, such as through pain management or CBT-I, yields long-term cognitive benefits is also crucial. This work could inform strategies for mitigating the dual burden of chronic pain and cognitive decline, particularly in older adults.

7.6.6 Could cognitive function predict pain?

Chronic pain may result from a dysfunctional learning response, where individuals possessing lower cognitive reserves are less capable of adapting to pain-related stressors, increasing their susceptibility to chronic pain[406]. Executive function, crucial for goal-directed behaviours and coping, could influence the transition from acute to chronic pain[364]. However, most studies focus on older adults, where pain and cognitive changes are intertwined with aging. Pain earlier in life, such as during childhood or adolescence, may disrupt cognitive development and predispose individuals to future pain[478], warranting investigation through longitudinal birth cohort studies.

7.6.6.1 Potential confounders and contrasting evidence

Mendelian Randomisation (MR) studies, however, challenge this assumption[187], suggesting that observed associations may stem from confounding factors like education and socioeconomic status[116; 284]. Failure to account for these factors in observational studies could lead to spurious associations between cognition and future pain.

7.6.7 Resolving the causation question

Longitudinal studies examining the interaction of pain and cognition across the life course, while accounting for important confounders, are important. However, randomised trials targeting pain with cognition as an endpoint, or vice versa, could clarify causality.

7.7 Causal relevance & need for randomised trials

Is nociplastic pain, exemplified by fibromyalgia, associated with cognitive impairment, and do pain severity and sleep disturbances play a role in this relationship? Using the Bradford Hill criteria as a framework[199], below I summarise the evidence and highlight key areas for future research.

7.7.1 Strength of association

The observed effect size is modest, with 3.5 centile lower executive function between individuals with and without chronic pain in UK Biobank. This effect, while not large, aligns with findings from other studies and underscores the subtle yet meaningful impact of nociplastic pain on cognitive performance. However, there was no association between chronic pain and cognitive decline.

7.7.2 Consistency and reproducibility

A cross-sectional association between nociplastic pain and cognitive impairment is consistently observed across both studies. This reproducibility, coupled with corroborating evidence from other fibromyalgia studies[38; 126; 127; 509], strengthens

the argument that nociplastic pain is associated with cognitive deficits. However, evidence for a longitudinal association is conflicting (**Table 1-1**).

7.7.3 Specificity

While nociplastic pain is associated with cognitive impairment, it is not specific to any single domain of cognition, as evidenced by deficits in both executive function and sustained attention[126; 127], and other domains such as memory[38]. This broader impact suggests that nociplastic pain exerts diffuse effects on cognitive processes, perhaps mediated by shared underlying mechanisms such as pain processing, and sleep disturbances, and anxiety.

7.7.4 Temporality

Temporality remains the most uncertain criterion in this association. In UK Biobank, there was no temporal relationship between nociplastic pain and cognitive decline. Although some longitudinal studies in chronic pain populations have reported accelerated cognitive decline[514], these findings are not universal[371; 470]. Furthermore, the relationships between fibromyalgia symptoms and cognitive performance in the PainLESS study were also cross-sectional, due to the study design. Thus, neither study demonstrates a temporal association between more severe nociplastic pain symptoms and subsequent decline in cognitive performance. This means that reverse causation cannot be excluded. It is possible that aspects of cognitive function, such as ability to direct attention away or towards pain, for example, may impact nociplastic pain severity. Alternatively, both nociplastic pain and cognitive performance may share underlying mechanisms, such as neuroinflammation or altered

CNS processing. Thus, future research employing longitudinal designs with repeated measures of pain and cognitive performance is needed to clarify the temporal relationship of pain and cognitive performance. Experimental studies, such as randomised trials, employing pain and cognition as endpoints would also be valuable to disentangle this relationship.

7.7.5 Biological gradient

There is robust evidence for a biological gradient. In UK Biobank, nociplastic pain severity showed a dose-response relationship with executive dysfunction. Similarly, in the PainLESS cohort, disease severity on the FIQR and associated symptoms demonstrated a gradient effect with cognitive impairment. Notably, pain severity and sleep disturbances also exhibited a dose-response relationship, including a U-shaped association with sleep duration, further supporting this criterion.

7.7.6 Plausibility, coherence, and experiment

The association between nociplastic pain, sleep, and cognition is both plausible and coherent with existing experimental evidence. Laboratory studies show that evoked pain and acute sleep deprivation impair cognitive performance[226; 373]. Additionally, improving sleep quality in insomnia has been shown to enhance self-reported, but not objectively measured, cognition[253]. Neuroimaging implicates DPMS connectivity, particularly between the PAG and amygdala, as a potential pathway linking pain processing to cognitive impairment. However, direct experimental evidence demonstrating that treating chronic pain alleviates cognitive impairments remains a key knowledge gap.

7.7.7 The need for randomised trials

The absence of experimental studies directly addressing whether treating nociplastic pain improves cognitive performance underscores the need for RCTs[515]. Observational studies, even when well-designed and adjusted for confounders such as age and education, remain susceptible to residual confounding and bias, especially when evaluating modest effect sizes like the relationship between pain and cognition[101]. The PainLESS study takes an important step toward addressing this gap by evaluating whether dCBT-I can improve both sleep quality and cognitive outcomes in fibromyalgia. Such trials will provide essential causal evidence to inform treatment strategies and advance our understanding of the bidirectional relationship between pain and cognition.

7.8 Strengths & limitations

7.8.1 Strengths

This thesis has several strengths. First, it examined the relationship between pain and cognition in two distinct and complementary populations: the large, population-based UK Biobank cohort and the clinically well-characterised PainLESS cohort.
A key contribution is the novel investigation of nociplastic pain severity as a continuous measure in relation to cognitive function at a population level. By concurrently examining a wide range of potential mediators, including sleep, pain, affect, cognitive difficulties, and energy/fatigue (SPACE symptoms), this work provides a nuanced understanding of the mechanisms underlying the observed cognitive impairments.

This thesis also incorporated a comprehensive range of confounders, enhancing the robustness of the findings. Additionally, it is among the first to examine both functional and structural connectivity within the DPMS at a population level, offering mechanistic insights into how pain may influence executive dysfunction.

Furthermore, the PainLESS study demonstrated the feasibility of conducting a trial of dCBT-I in a fibromyalgia population, achieving acceptable recruitment, engagement, and follow-up rates. Importantly, this study will be one of the first trials of dCBT-I in fibromyalgia, as well as the first trial of CBT-I to examine cognition as an endpoint.

7.8.2 Limitations

In the UK Biobank study, the relatively short follow-up period may have constrained the ability to detect long-term cognitive changes, despite its large sample size. Meanwhile, a healthy volunteer bias—predominantly white, British, healthier, and better educated participants—limits generalisability[441]. Similarly, the female preponderance in the PainLESS study, given the known sex differences in nociplastic pain observed in UK Biobank, reduces the generalisability of findings to male populations. Selection bias is an issue in both studies, due to attrition bias in UK Biobank, and poor control matching in the PainLESS study. The PainLESS study also had a relatively small sample size, which may have limited its statistical power to detect smaller associations or explore subgroup differences. However, replication of key findings in both UK Biobank and the PainLESS study, provides reassurance of the robustness of the key findings.

Conceptual limitations of nociplastic pain and its overlap with neuropathic pain further complicate the interpretation of findings[99]. While the FMI was used as a proxy for nociplastic pain severity, there are no validated measures of nociplastic pain. Pain

phenotyping in UK Biobank was limited, which were addressed in the PainLESS study by including participants with a clinical diagnosis of fibromyalgia confirmed by a clinician. Information bias is another concern, particularly regarding self-reported measures of sleep and medication use. It is worth noting that pain, by its nature, is a subjective experience and inherently self-reported. Although a wide range of confounders were adjusted for, residual confounding remains a possibility.

The reliance on rs-fMRI data in UK Biobank is another limitation, as the short multiband imaging protocol was not optimised for brainstem regions like the PAG, potentially underestimating relevant features. Finally, objective sleep measures (e.g., actigraphy and PSG) and task-based fMRI were not included but represent important avenues for future research.

7.9 Clinical implications and future research

7.9.1 Clinical implications

This thesis has several clinical implications. Digital CBT-I shows promise for addressing sleep and cognitive impairment in fibromyalgia and could be broadly applied to other nociplastic pain conditions where sleep disturbance is common[230]. If effective, it may be integrated into pain management programs, such as the *Optimise* programme in Oxford.

The use of Connectome Predictive Modelling (CPM) with rs-fMRI offers a practical way to identify biomarkers of cognitive impairment and could enhance precision in clinical trials[409]. PAG-amygdala connectivity, identified as a potentially important pathway for pain and cognitive dysfunction, presents a potential therapeutic target for interventions like deep brain stimulation (DBS), transcranial direct current stimulation

(tDCS), transcranial magnetic stimulation (TMS) or transcranial ultrasound (TUS), warranting further exploration.

The FMI demonstrated utility in measuring nociplastic pain severity and should be further evaluated in clinical and population-based studies to better understand its broader health implications. Additionally, the NVT, sensitive to sustained attention deficits in fibromyalgia, offers an easy-to-implement tool for future clinical trials assessing cognitive outcomes.

7.9.2 Future research direction

7.9.2.1 Trial of dCBT-I in fibromyalgia

Building on the feasibility study conducted for this thesis, a trial of *Sleepio* in fibromyalgia is underway, with post-treatment follow-up set for completion in Spring 2025. This study aims to determine whether improving sleep quality can alleviate cognitive impairments, potentially establishing dCBT-I as part of standard care for fibromyalgia and other nociplastic pain conditions.

7.9.2.2 Neural markers of sustained attention in evoked pain vs. fibromyalgia

The intriguing results regarding CPM-derived sustained attention markers in fibromyalgia warrant further exploration. A *WIN* Seed Grant-funded pilot study will compare NVT-derived neuromarkers in healthy adults under evoked tonic pain with those in fibromyalgia patients. This will explore whether sustained attention under pain conditions differs from typical patterns, deepening our understanding of pain-specific alterations in attention networks.

7.9.2.3 Impact of CBT-I on movement behaviours in fibromyalgia

Exercise is a cornerstone of fibromyalgia management, known to benefit both sleep and cognition[2]. However, fear of movement is prevalent in fibromyalgia, complicating adherence to physical activity interventions[474]. An MRC-funded study commencing in 2025 will examine movement behaviours before and after dCBT-I using virtual reality (VR), alongside PSG and ambulatory assessments of movement, sleep, and pain. Comparing self-reported sleep measures with actigraphy and PSG will clarify how sleep disruptions contribute to cognitive impairment, providing a foundation for targeted interventions. This research aims to address barriers to physical activity in fibromyalgia and advance understanding of the interplay between these factors.

7.9.2.4 Expanding UK Biobank analyses

The UK Biobank offers ongoing opportunities for future research. The recent release of detailed sleep questionnaires and forthcoming health record linkages will allow exploration of more nuanced sleep phenotypes and their relationships with pain and cognition at a population level. Improved medication data will also enhance the precision of these analyses. As the UK Biobank cohort ages, it will enable investigations into the associations between FMI, incident dementia, and other clinical outcomes, extending the findings of this thesis into new domains.

7.9.2.5 Other research priorities

Future work should explore cognitive outcomes across different pain phenotypes. While fibromyalgia is classically associated with cognitive impairment, other pain types, such as neuropathic pain, may also exert pronounced effects on cognition[215].

7.10 Concluding remarks

This thesis underscores the complex relationship between nociplastic pain, sleep disturbance, and cognitive impairments, particularly in fibromyalgia. Pain severity and abnormal sleep emerged as key factors in executive dysfunction and sustained attention deficits, while altered DPMS connectivity, especially between the PAG and amygdala, provides mechanistic insight into this relationship. The feasibility of dCBT-I as a scalable intervention offers a promising path to improve sleep and cognition in fibromyalgia. These findings highlight the need for future research to explore longitudinal trajectories, test targeted therapies, and expand to diverse clinical populations, paving the way for more effective and personalised approaches to mitigate the dual burden of chronic pain and cognitive dysfunction.

A Appendix A: Chapter 2

A.1 Search Strategy

PubMed, MEDLINE, Embase, CINAHL, Cochrane CENTRAL and the International Trial Registries (The World Health Organisations trials portal (ICTRP)) will be searched using the following search string for randomised controlled trials:

PubMed, MEDLINE

fibromyalgia[Title]) AND (sleep) AND (CBT OR cognitive behavioural therapy OR pharmacological OR drugs OR benzodiazepine OR sedating antidepressants OR sedating antihistamine or amphetamines OR SSRI OR SNRI)

Embase

1. Fibromyalgia* :ab,ti,kw
2. Sleep* :ab, ti, kw
3. (CBT* OR cognitive behavioural therapy)
4. (pharmacological* OR drugs* OR benzodiazepine* OR sedating antidepressants* OR sedating antihistamine* OR amphetamines* OR SSRI* OR SNRI*) :ab,ti,kw
5. Randomized controlled trial* :pt
6. #5 or #6
7. #3 and #4 and #8 and #9

Appendix A

CINAHL

fibromyalgia[Title])

AND (sleep) [Abstract]

AND (CBT OR cognitive behavioural therapy OR pharmacological OR drugs OR benzodiazepine OR sedating antidepressants OR sedating antihistamine or amphetamines OR SSRI OR SNRI) [Title]

Filters: articles

Cochrane CENTRAL

Fibromyalgia [Title])

AND (sleep) [Title Abstract Keyword]

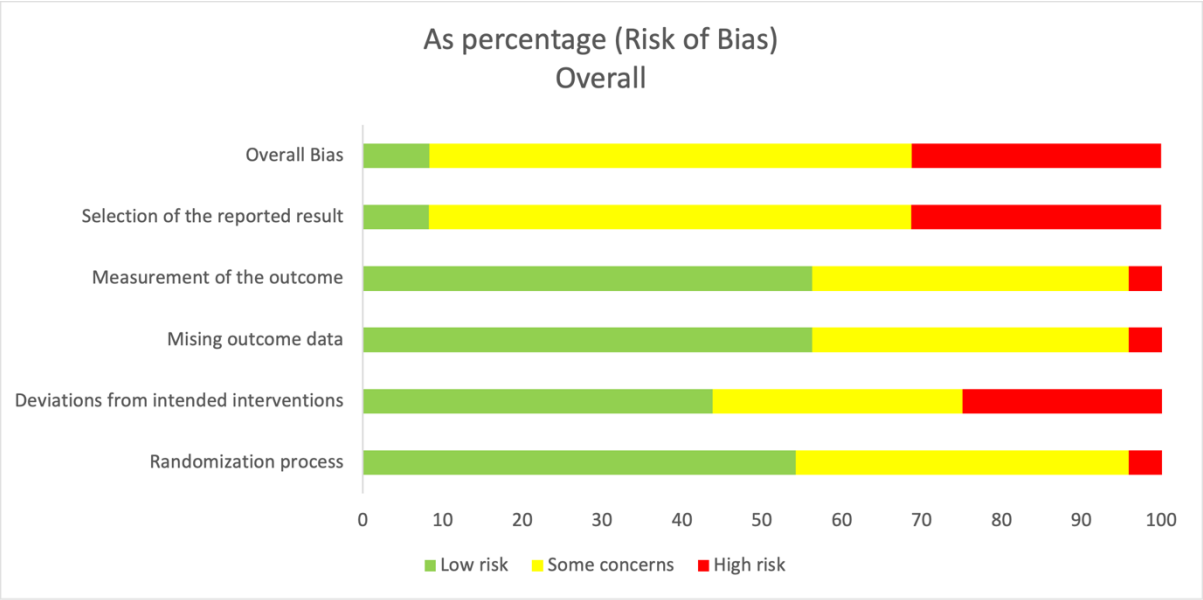
AND (CBT OR cognitive behavioural therapy OR pharmacological OR drugs OR benzodiazepine OR sedating antidepressants OR sedating antihistamine or amphetamines OR SSRI OR SNRI) [Title]

Filters: trials

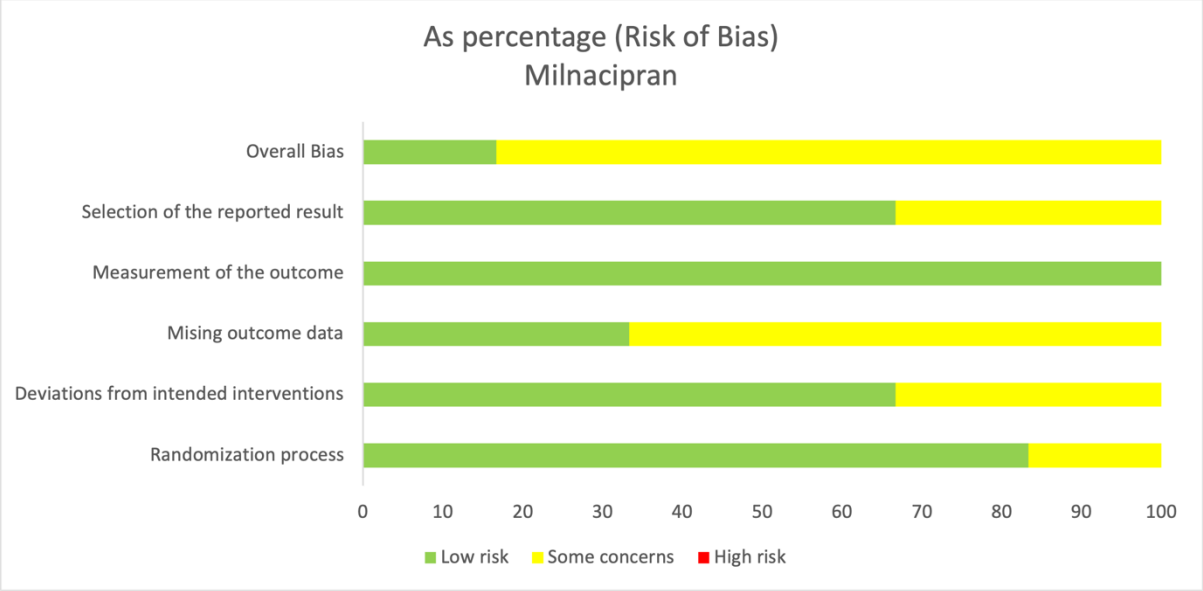
International trials registers

(sleep) AND (CBT OR cognitive behavioural therapy OR pharmacological OR drugs OR benzodiazepine OR sedating antidepressants OR sedating antihistamine or amphetamines OR SSRI OR SNRI) | Completed Studies | Studies With Results | Interventional Studies | Fibromyalgia | Adult, Older Adult | Last update posted from 01/01/1980 to 01/02/2025

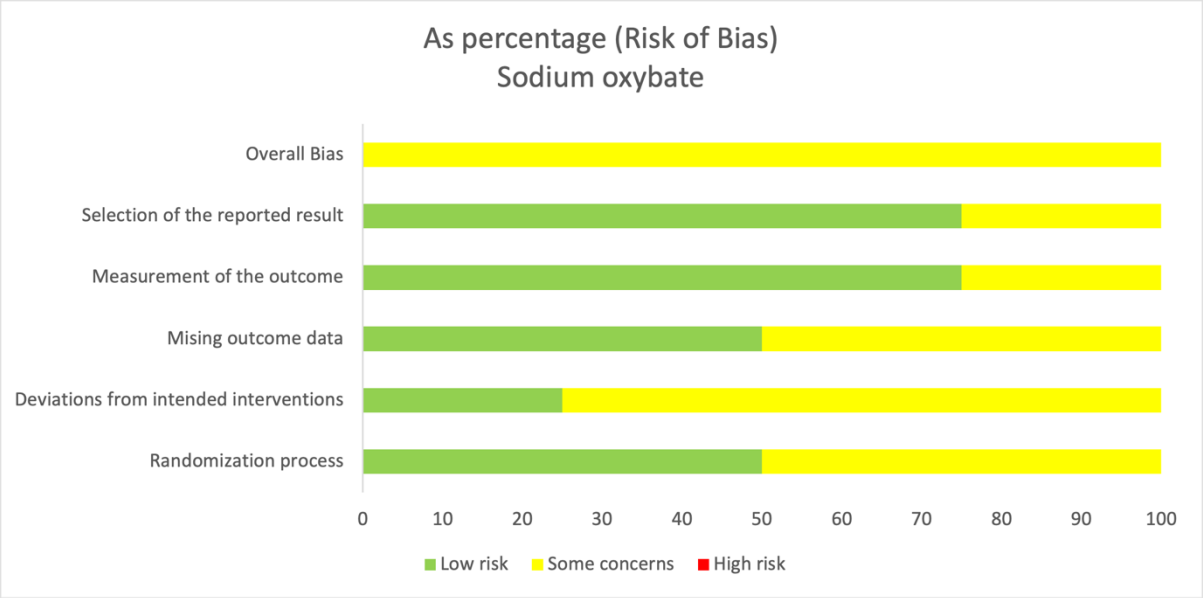
A.2 Risk of Bias assessment



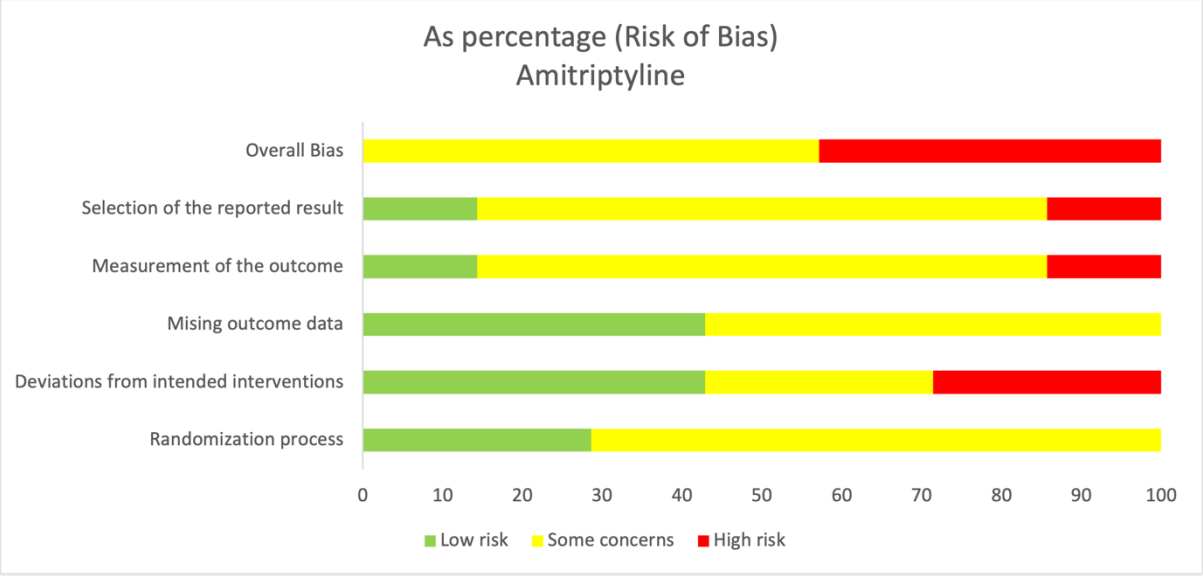
Supplementary Figure A-1. ***Overall Risk of Bias for All Included Studies*** *This figure provides a comprehensive summary of risk of bias across all included studies, both pharmacological and CBT.*



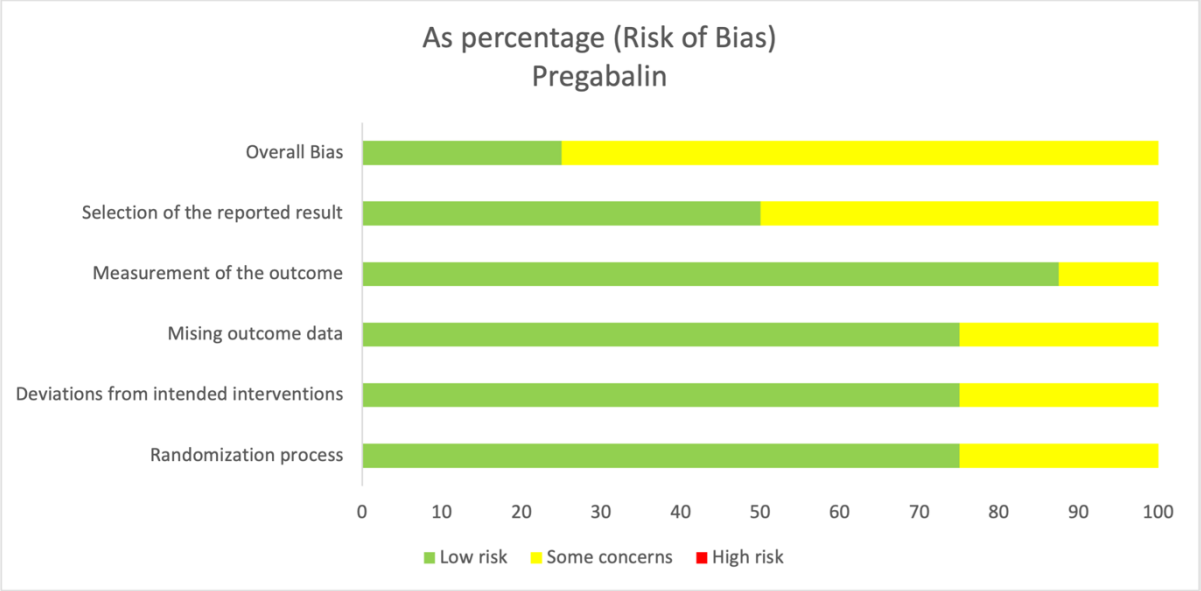
Supplementary Figure A-2. ***Risk of Bias for Milnacipran Studies.*** *This figure shows the distribution of risk of bias assessments across different domains for studies involving Milnacipran. The majority of studies demonstrate a low risk of bias in randomization, measurement of outcomes, and deviations from intended interventions, while "some concerns" were noted primarily in the selection of reported results. Overall, these studies predominantly show low risk with minor concerns, indicating robust study designs with minimal bias.*



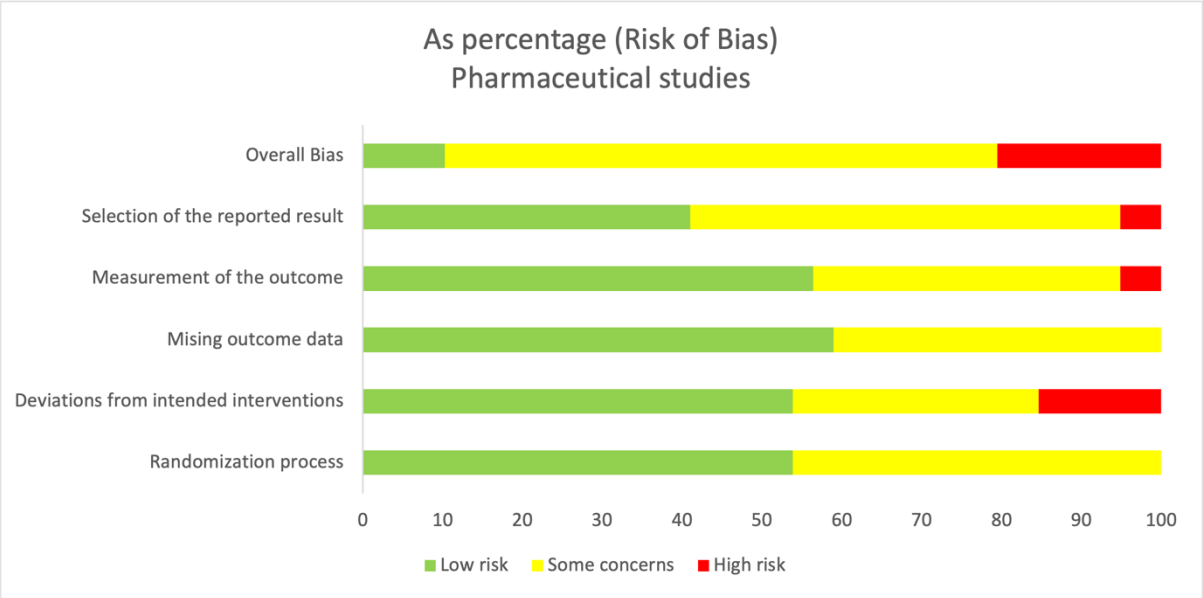
Supplementary Figure A-3. ***Risk of Bias for Sodium Oxybate Studies.*** *The risk of bias profile for Sodium Oxybate studies is illustrated here, revealing predominantly "some concerns" in multiple domains, especially in the selection of reported results and deviations from intended interventions. The figure highlights an even distribution between low risk and some concerns in the measurement of outcomes and missing outcome data, with an overall moderate level of bias due to prevalent concerns across domains.*



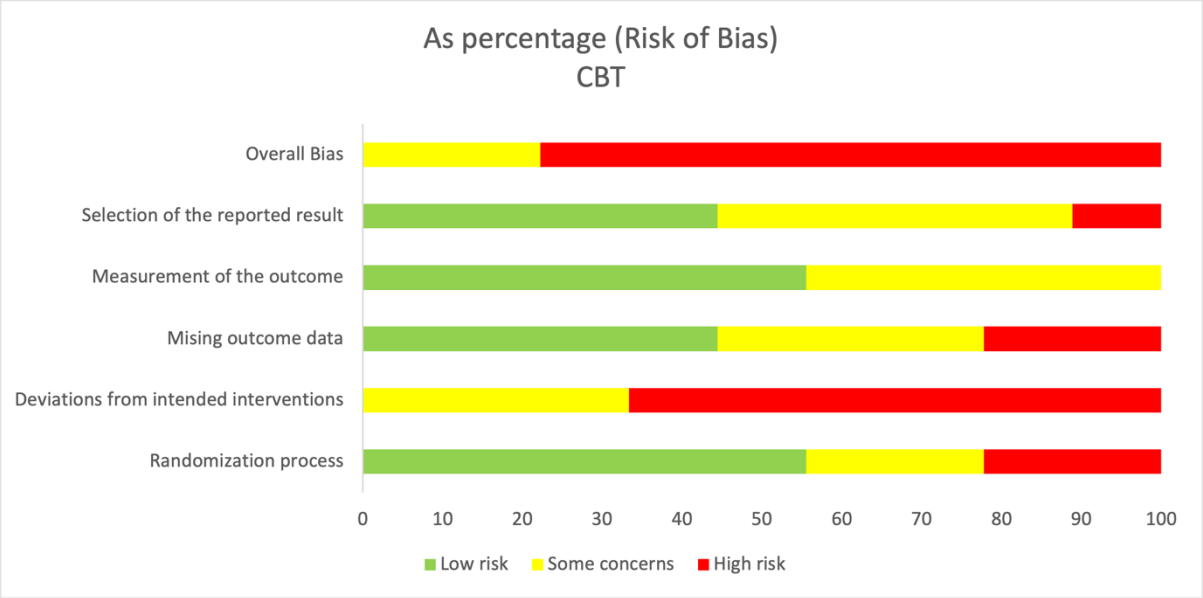
Supplementary Figure A-4. ***Risk of Bias for Amitriptyline Studies.*** *This figure presents the risk of bias in studies evaluating Amitriptyline. A significant number of these studies exhibit "some concerns" and high risk of bias across domains, notably in the selection of reported results and deviations from intended interventions. High risk is particularly pronounced in the overall bias and deviations from interventions, suggesting methodological limitations in these studies.*



Supplementary Figure A-5. ***Risk of Bias for Pregabalin Studies.*** *This figure depicts the risk of bias assessments across domains for Pregabalin studies, with a large proportion of low risk in most domains, particularly randomization and measurement of outcomes. Some concerns are noted in deviations from intended interventions and selection of reported results, indicating that while the studies are generally well-conducted, there are minor methodological considerations to account for.*



Supplementary Figure A-6. ***Risk of Bias in Pharmacological Studies.*** *This figure aggregates risk of bias across all pharmacological studies included in the review, encompassing drugs like Milnacipran, Pregabalin, and Amitriptyline. The chart indicates a predominance of "some concerns" in the selection of reported results and deviations from intended interventions. A smaller portion of studies exhibits high risk, primarily impacting the overall bias assessment, while randomization and missing data are generally rated at low risk.*

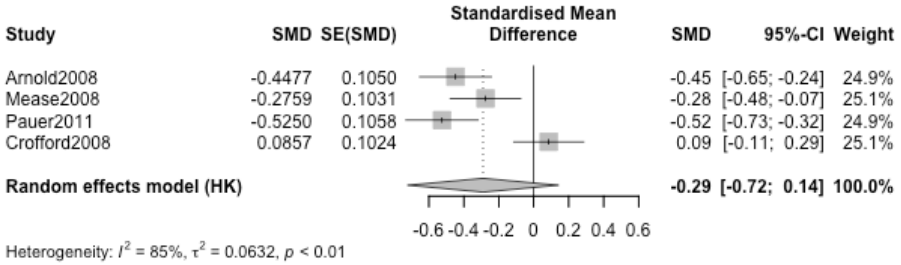


Supplementary Figure A-7. ***Risk of Bias for Cognitive Behavioural Therapy (CBT) Studies*** *The risk of bias for CBT studies is illustrated here, highlighting a pronounced high risk in several domains, especially deviations from intended interventions and overall bias. The majority of studies demonstrate concerns in multiple areas, with high risk most frequent in deviations from intended interventions. This profile suggests that CBT studies face greater methodological challenges relative to pharmacological studies.*

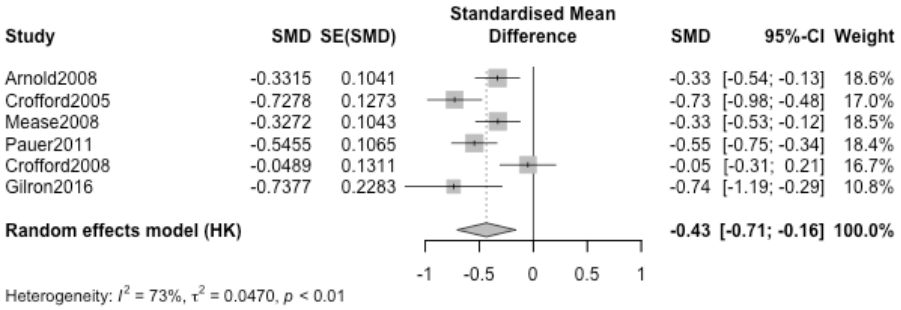
A.3 Sensitivity analyses for meta-analysis:

A.3.1 Pregabalin

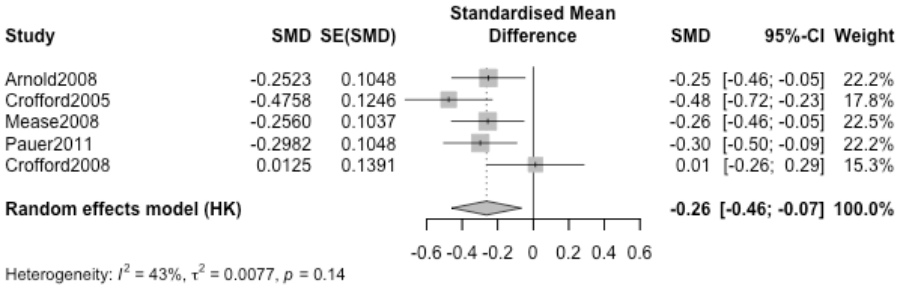
The sensitivity analyses of pregabalin's effects on fibromyalgia symptoms reveal consistent findings across different dosage levels and study types, highlighting variations in effectiveness depending on the criteria applied. For instance, higher dosages such as 600 mg and 450 mg generally show more pronounced effects compared to lower doses like 300 mg, aligning with an expected dose-response relationship. Excluding crossover trials slightly reduces the pooled effect size, which indicates that crossover designs might amplify treatment effects due to within-subject comparisons. Across all analyses, moderate-to-high heterogeneity (I^2 values ranging from 43% to 85%) suggests variability among studies, likely due to differences in patient populations, study designs, and outcome measures.



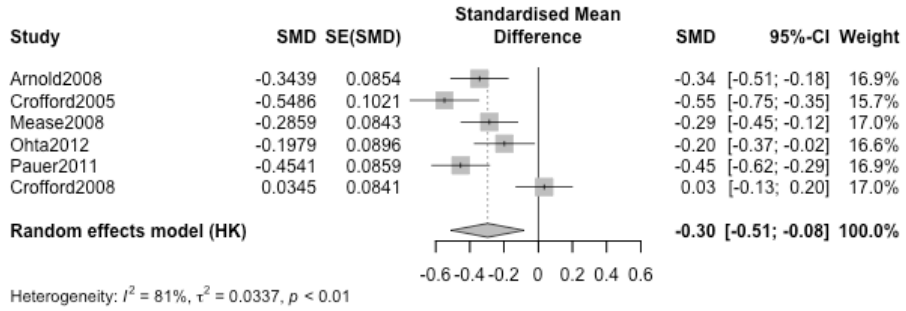
Supplementary Figure A-8. Forest plot showing the sensitivity analysis for studies using 600 mg of pregabalin in fibromyalgia treatment. The pooled standardized mean difference (SMD) is -0.29 (95% CI: -0.72 to 0.14), with substantial heterogeneity (I^2=85%, p < 0.01). This analysis reflects significant variation among studies regarding pregabalin's efficacy at this dose.



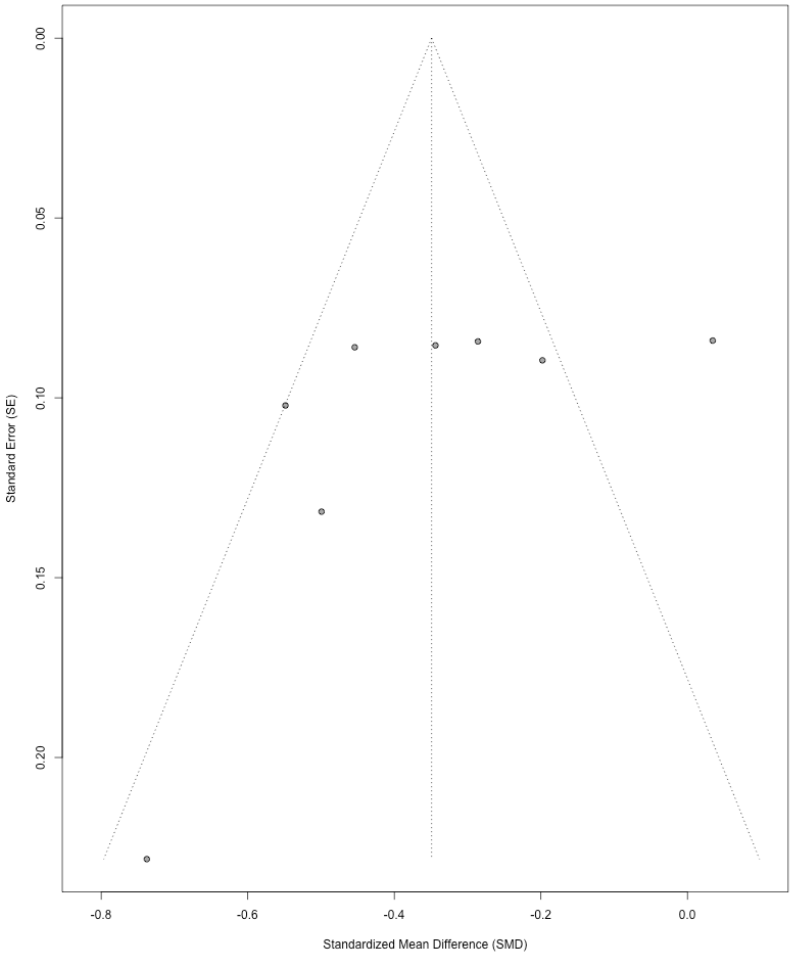
Supplementary Figure A-9. Forest plot for 450 mg pregabalin sensitivity analysis including all study designs. The pooled SMD is -0.43 (95% CI: -0.71 to -0.16), with moderate heterogeneity (I^2=73%, p < 0.01), indicating a significant, moderate effect of pregabalin at this dose.



Supplementary Figure A-10. Forest plot displaying the sensitivity analysis for 300 mg pregabalin in fibromyalgia treatment. The pooled SMD is -0.26 (95% CI: -0.46 to -0.07), with lower heterogeneity (I^2=43%, p=0.14), suggesting a modest effect with relatively consistent findings across studies at this dose.

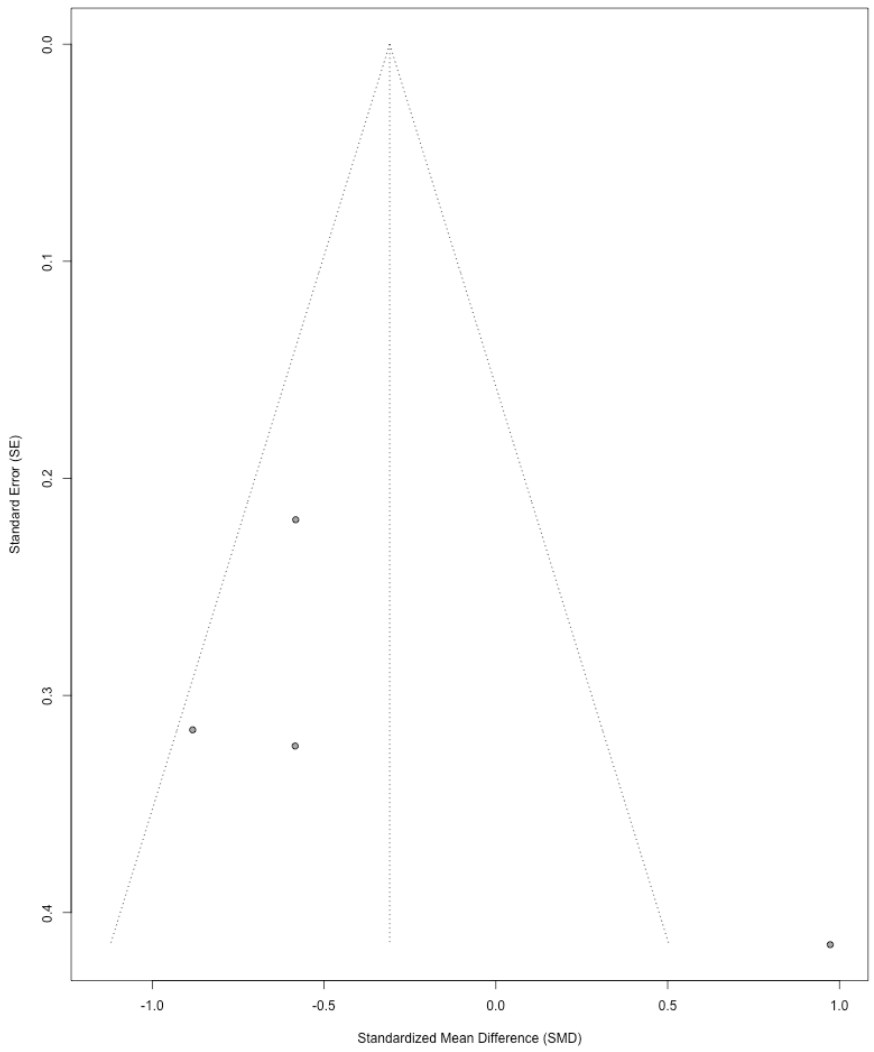


Supplementary Figure A-11. Forest plot showing the pooled sensitivity analysis of pregabalin doses in fibromyalgia, excluding crossover studies. The pooled SMD is -0.30 (95% CI: -0.51 to -0.08), with high heterogeneity (I^2=81%, p < 0.01). Excluding crossover designs yields a moderate, statistically significant effect, indicating consistent efficacy of pregabalin across different doses.



Supplementary Figure A-12. Funnel plot assessing publication bias for pooled studies examining pregabalin's effect on fibromyalgia symptoms. The plot displays standardized mean differences (SMD) against standard errors (SE). Symmetry around the vertical line, representing the pooled effect size, suggests minimal publication bias. However, slight asymmetry at the lower left indicates potential for small-study effects or selective reporting, as smaller studies with larger effects are more prominent on the left side of the plot. Further investigation may be needed to confirm any bias.

A.3.2 Amitriptyline



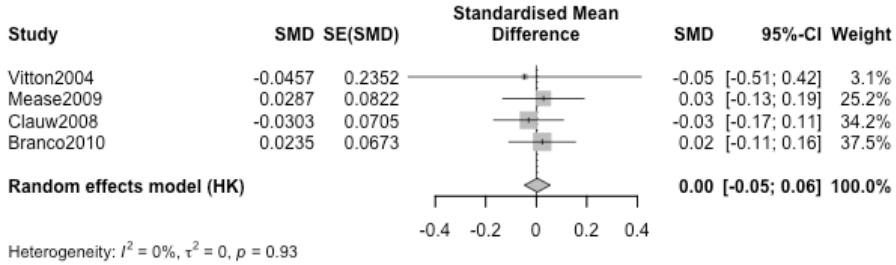
Supplementary Figure A-13. Funnel plot evaluating publication bias in studies investigating the effect of amitriptyline on fibromyalgia symptoms. The plot shows standardized mean differences (SMD) plotted against standard errors (SE). The symmetry around the vertical line, which represents the overall effect size, suggests low publication bias. However, some asymmetry on the right side of the plot, where a small study displays a high positive effect size, may indicate the presence of outlier effects or publication bias. Further assessment is warranted to confirm the robustness of these findings.

A.3.3 Milnacipran

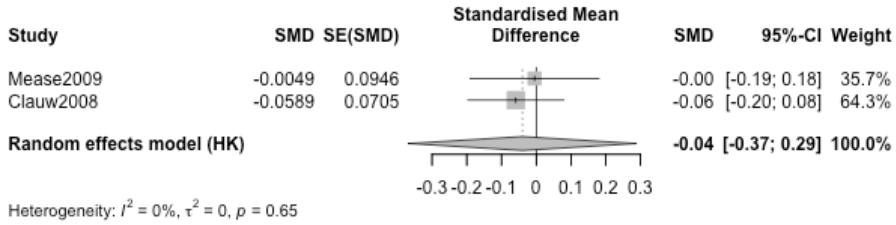
The sensitivity analyses for milnacipran, examining different dosages and study designs, showed small and statistically non-significant effects on sleep outcomes for fibromyalgia patients. When separated by dosage, both 100 mg and 200 mg groups revealed minor effects, with overlapping confidence intervals indicating no clear advantage of a higher dose. Additionally, heterogeneity across studies was low, as reflected by I^2 values close to 0%, suggesting consistency in findings across the milnacipran studies included in the analysis. However, the pooled analysis still demonstrated minimal overall effect, suggesting that milnacipran may have limited efficacy in improving sleep outcomes for this population.

The funnel plot for the pooled milnacipran analysis did not display asymmetry, indicating a low likelihood of publication bias, although the limited number of studies restricts a definitive conclusion on this aspect.

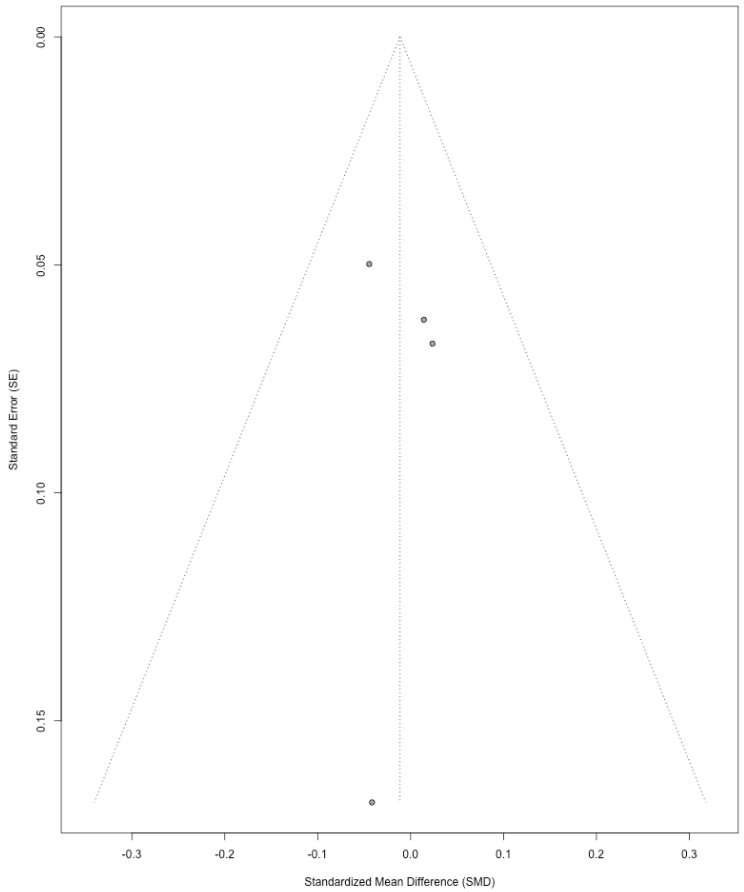
These findings underscore that, despite its use, milnacipran does not significantly improve sleep disturbances in fibromyalgia, regardless of dosage, with consistency across studies confirming this limited effect.



Supplementary Figure A-14. Forest plot of studies evaluating 200 mg milnacipran for fibromyalgia. Standardized mean differences with 95% confidence intervals indicate minimal efficacy, with low heterogeneity (I^2=0%), suggesting consistent effects across studies



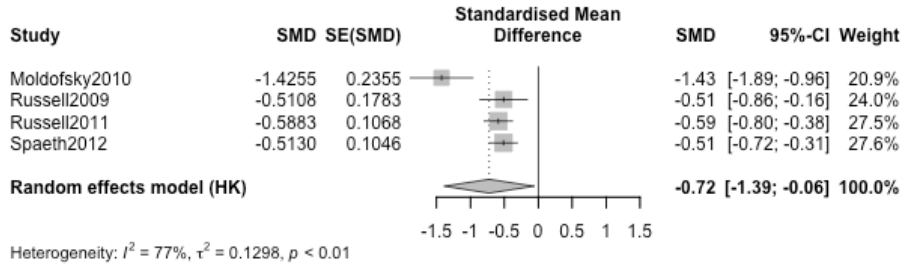
Supplementary Figure A-15. Forest plot of studies evaluating 100 mg milnacipran for fibromyalgia. Each study's standardized mean difference (SMD) is shown with 95% confidence intervals. Low heterogeneity (I^2=0%) suggests consistent findings across studies



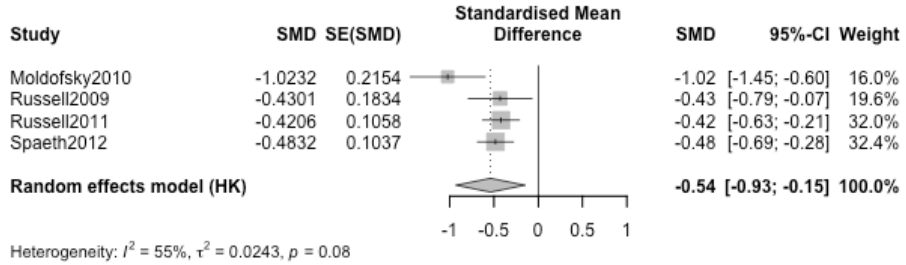
Supplementary Figure A-16. Funnel plot of standardized mean differences (SMD) for pooled milnacipran studies assessing efficacy in fibromyalgia. Symmetrical distribution of studies suggests minimal publication bias.

A.3.4 Sodium Oxybate

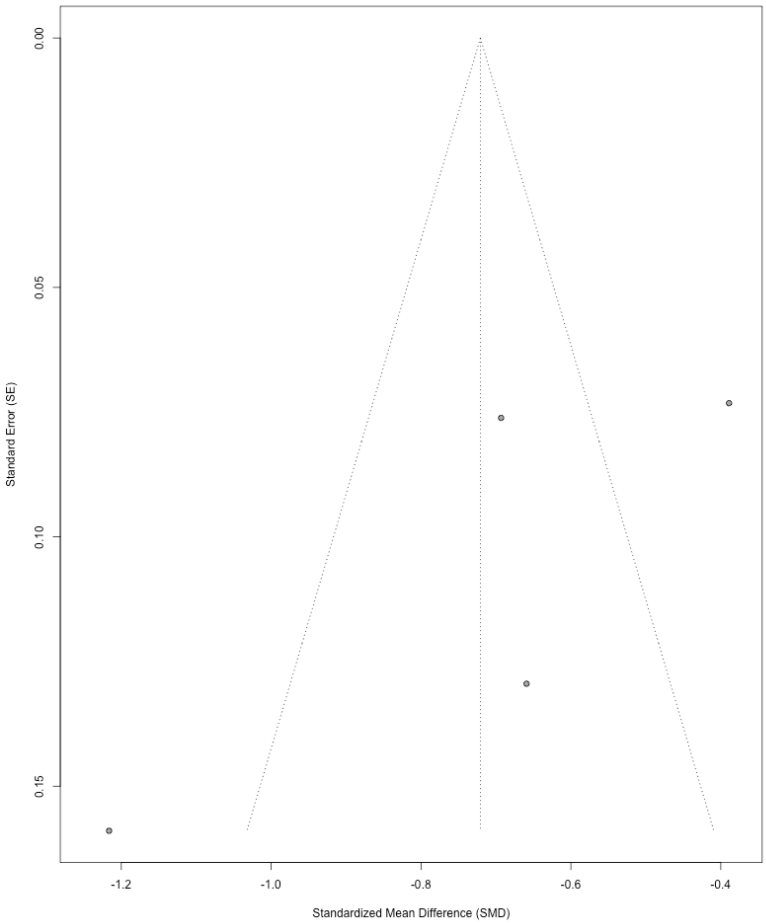
The sensitivity analyses for sodium oxybate indicate that both 6.0 g and 4.5 g dosages have significant positive effects on sleep outcomes in fibromyalgia. The 6.0 g dose shows a larger effect size (SMD=-0.72), though with high heterogeneity (I2=77%I2=77%), while the 4.5 g dose has a moderate effect (SMD=-0.54) with moderate heterogeneity (I2=55%I2=55%). The funnel plot for pooled studies shows no clear asymmetry, suggesting low risk of publication bias. Overall, sodium oxybate appears effective, with higher doses yielding greater benefits, though variability between studies suggests patient characteristics may influence results.



Supplementary Figure A-17. ***Forest Plot of Sodium Oxybate 6.0 g Sensitivity Analysis****: A forest plot displaying the standardized mean difference (SMD) for sodium oxybate at a 6.0 g dosage across multiple studies. The pooled SMD is -0.72 (95% CI: -1.39 to -0.06), indicating a strong effect. High heterogeneity (I2=77%I2=77%) suggests variability in outcomes across studies.*

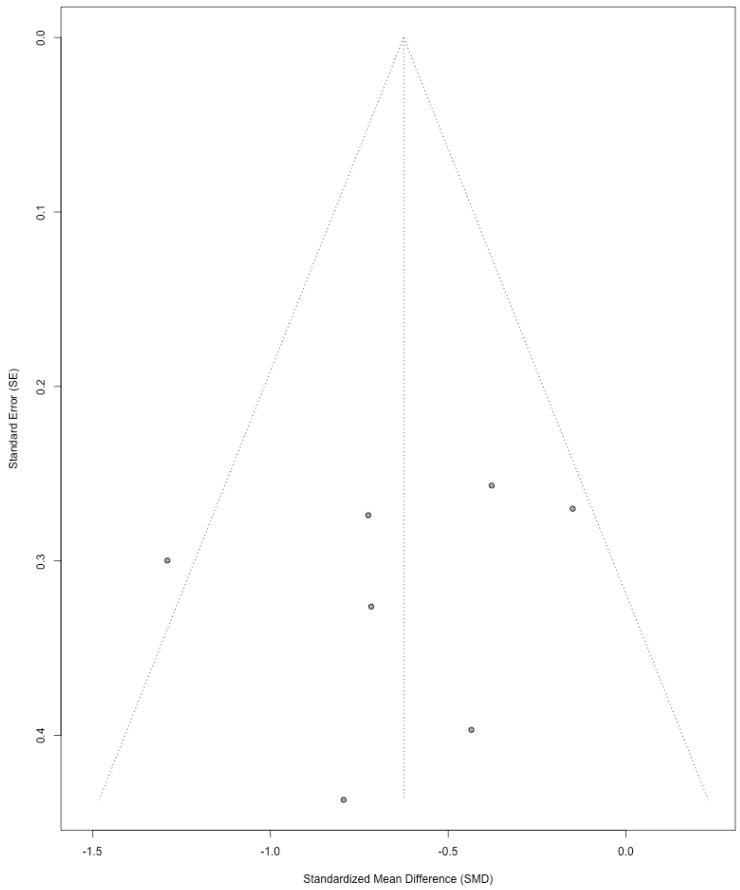


Supplementary Figure A-18. ***Forest Plot of Sodium Oxybate 4.5 g Sensitivity Analysis****: A forest plot showing the SMD for sodium oxybate at a 4.5 g dosage across studies. The pooled SMD is -0.54 (95% CI: -0.93 to -0.15), demonstrating a moderate effect with moderate heterogeneity (I2=55%I2=55%), suggesting some consistency in findings with a slight variation between studies.*

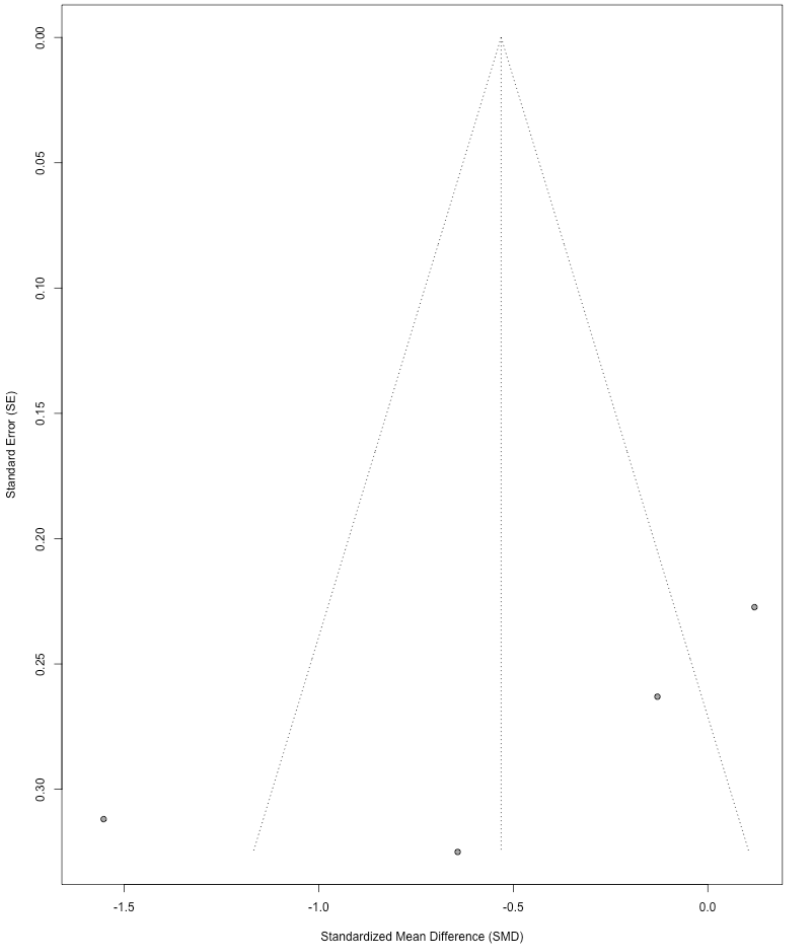


Supplementary Figure A-19. ***Funnel Plot of Pooled Sodium Oxybate Studies****: A funnel plot evaluating the potential for publication bias in studies of sodium oxybate for fibromyalgia-related sleep issues. The symmetrical distribution of studies around the pooled effect estimate suggests a low likelihood of publication bias.*

A.3.5 Cognitive Behavioural Therapy



Supplementary Figure A-20. Funnel plot for the pooled analysis of Cognitive Behavioural Therapy for insomnia (CBT-I) interventions. Each point corresponds to a study's standardized mean difference (SMD) and standard error (SE). The plot's symmetry suggests minimal publication bias, reinforcing the reliability of the pooled CBT-I effect size.



Supplementary Figure A-21. Funnel plot for the pooled analysis of Cognitive Behavioural Therapy for pain (CBT-P) interventions. Each point represents an individual study's standardized mean difference (SMD) plotted against its standard error (SE). Slight asymmetry suggests potential publication bias favoring larger effects, though limited study number restricts interpretability.

B Appendix B: Chapter 3

B.1 Variables used in UK Biobank analysis

Appendix B

Variable	UKB Datafield	Instance	Comments
Age	21003	2	
Sex	31	0	
Ethnicity	21000	2	Binarised to white or non-white. Imputed with instance 0 if missing at 2
Townsend Deprivation Index	22189	0	
Education	6138	2	Binarised to University Degree and No Degree. Instance 0 or 10722 used if 6138 missing.
Employment status	6142	2	Binarised to employed or not employed
Smoking	20116	2	Binarised to current smoking or not current smoker
Alcohol use	1558	2	Binarised to current alcohol use or no current alcohol use
BMI	21001	2	Instance 0 or 23104 used if 21001 missing
Sleep duration	1160	2	
Abnormal sleep duration	1160	2	Binarised to <7 & >9 or 7-9
Opioid use	20003	2	See below for codes used to identify opioids
Tricyclic antidepressant use	20003	2	See below for codes used to identify TCAs
Gabapentinoid use	20003	2	See below for codes used to identify gabapentinoids
Exclusion	20002	0	If contained codes: 1262 (dementia), 1263 (Parkinson's), 1289 (psychosis), or 1291 (bipolar disorder)
Chronic pain	120019	PQ	Answered "Yes"
Widespread Pain Index	120039	PQ	Sum of the number of pain areas. Those who reported “Undisclosed area” were regarded as missing
Fatigue	120040	PQ	
Unrefreshing sleep	120041	PQ	
Cognitive difficulties	120042	PQ	
Abdominal pain	120043	PQ	
Depression	120044	PQ	
Headache	120045	PQ	
Symptom ***Severity*** Scale		PQ	sum of 120039-120045
Fibromyalgia Index		PQ	Sum of Widespread Pain Index and Symptom Severity Scale
Pain severity (NRS)	120022 & 12086	PQ	
Depression (PHQ-9)	120104-120112	PQ	Sum of 120104-120112
Anxiety (GAD-7)	29058-29064	MWBQ	sum of 29058-29064
Fatigue Severity Scale (FSS)	120119-120127	PQ	Sum of 120119-120127, not answered if 120018 is "No" and 120040 is "No problem". In that case the variable was set at the minimum value (i.e. 9)
Neuropathic Pain (DN4)	120046-120052	PQ	Sum of 120046-120052. Only answered participant reported chronic pain in a body site

Variable	UKB Datafield	Instance	Comments
			(not answered if participant reported chronic pain "all over the body"
Cognitive outcomes			
Trail making test at baseline		**2**	**Difference between trail A & B**
Time taken for trail A	6348	2	
Time taken for trail B	6350	2	
Digit symbol substitution test at baseline			**Proportion of attempts correct**
Number of attempts	23323	2	
Number correct	23324	2	
Matrix Pattern test at baseline			**Proportion of attempts correct**
Number of attempts	6374	2	
Number correct	7373	2	
Trail making test at follow-up			**Difference between trail A & B**
Time taken for trail A	20156	1	
Time taken for trail B	20157	1	
Digit symbol substitution test at follow-up			**Proportion of attempts correct**
Number of attempts	20195	1	
Number correct	20159	1	
Matrix Pattern test at follow-up			**Proportion of attempts correct**
Number of attempts	20761	1	
Number correct	20760	1	
Baseline date	53	2	
Date of Pain Questionnaire	120128	PQ	
Matrix Pattern Test date	20765	1	
Symbol Digit Substitution test date	20137	1	
Trail Making Test date	20136	1	
Date of Follow-up Cognition			Average of 20765, 20137, and 20136
Age at pain assessment			Derived from field 31 and date of Pain Questionaire
Follow-up time from baseline to pain questionnaire			The difference between baseline date (53) and pain questionnaire date (120128)
Follow-up time from baseline to follow-up cognition			The difference between pain questionnaire date (120128) and follow-up cognition date

Supplementary Table B-1. Field IDs of variables from UK Biobank used in analysis

Appendix B

Variable	Codes		
Opioid	1141170964	1141170966	1141170972
	1141171052	1141171054	1141171066
	1140856422	1140856354	1140856356
	1140882392	1140882268	1140862988
	1140871402	1140884464	1140878030
	1141190956	1140925778	1140868286
	1140871906	1140871910	1140871902
	1140871926	1140871920	1140871924
	1141190656	1141165512	1141169692
	1141192990	1141192992	1141192994
	1140871726	1140871776	1140871730
	1140871798	1140871728	1140871782
	1140871684	1141151000	1141168650
	1141189008	1141189064	1141189010
	1140871682	1140928262	1140928266
	1140880956	1141157470	1140879212
	1141172878	1141172880	1141172882
	1140856356	1140884388	1141100000
	1141171038	1141171048	1141171050
	1140856406	1140856416	1140856418
	1140856442	1140856454	1140856456
	1140884444	1140884452	1140865654
	1140856406	1141175200	1140882394
	1140856422	1140910402	1140871908
	1140856456	1140856454	1140856458
	1140884460	1140862910	1140855802
	1141168794	1140864070	1140910376
	1140871692	1140882116	1140882406
	1140871708	1140864632	1140871796
	1140871722	1140927388	1140927384
	1140856340	1141189068	1141189066
	1140856442	1141168648	1140871688
	1140856214	1140923346	1140923344
	1140880942	1141172936	1141172938
	1140911836	1140911830	1140911832
	1140856420	1140882114	1141167748
	1140856458	1141192996	1141168122
	1141187304	1140871786	1140923350
	1140882396	1140871780	1141172876
	1140871904	1140871686	1140911834
	1140864536		

Variable	Codes		
Tricylic antidepressants	1140879616	1140867948	1140867938
	1140867658	1140867818	1140867662
	1140867668	1140867600	
Gabapentinoids	1141200004	1140872228	1141200072
	1140872236		

Supplementary Table B-2. Codes used to derive self-reported analgesia use from questionnaire at time of first imaging visit.

All codes derived from field ID 20002 at instance 2 in UK Biobank.

B.2 Baseline characteristics

	Total	No Chronic pain	Chronic pain
	(N=18898)	(N=8876)	(N=10022)
Sex			
Female	9884 (52 %)	4300 (48 %)	5584 (56 %)
Male	9014 (48 %)	4576 (52 %)	4438 (44 %)
Age (years)			
Mean (SD)	64.5 (7.35)	64.5 (7.38)	64.6 (7.33)
Townsend Deprivation Index			
Mean (SD)	-1.91 (2.70)	-1.97 (2.67)	-1.85 (2.73)
Marital status			
Married/Partner	14301 (76 %)	6791 (77 %)	7510 (75 %)
Not married	4534 (24 %)	2063 (23 %)	2471 (25 %)
Employment status			
Employed	7244 (38 %)	3515 (40 %)	3729 (37 %)
Retired	10938 (58 %)	5067 (57 %)	5871 (59 %)
Unemployed/Other	684 (4 %)	282 (3 %)	402 (4 %)
White ethnicity, %	97.7%	97.8%	97.7%
University degree, %	54.1%	56.6%	51.9%
Current tobacco use, %	2.76%	2.68%	2.83%
Alcohol Use			
Never	1160 (6 %)	520 (6 %)	640 (6 %)
Rarely	4007 (21 %)	1771 (20 %)	2236 (22 %)
Weekly	10459 (55 %)	5015 (57 %)	5444 (54 %)
Daily	3235 (17 %)	1556 (18 %)	1679 (17 %)
Body Mass Index (kg/m2)			
Mean (SD)	26.4 (4.43)	25.9 (4.11)	26.8 (4.66)
Fibromyalgia Index (0-31)			
Mean (SD)	3.52 (3.42)	1.94 (1.91)	4.93 (3.82)
Widespread Pain Index (0-19)			
Mean (SD)	1.24 (1.91)	0.281 (0.767)	2.09 (2.20)
Symptom Severity Scale (0-12)			
Mean (SD)	2.28 (2.07)	1.66 (1.63)	2.83 (2.26)
Sleep duration, self reported			
Mean (SD)	7.16 (1.00)	7.22 (0.952)	7.10 (1.04)
Sleep duration, seld reported			
<7 hours	4341 (23 %)	1762 (20 %)	2579 (26 %)
7-9 hours	13240 (70 %)	6507 (73 %)	6733 (67 %)
>9 hours	1243 (7 %)	576 (6 %)	667 (7 %)
Pain intensity, NRS (0-10)			

	Total	No Chronic pain	Chronic pain
Mean (SD)	3.66 (2.57)	NA (NA)	3.66 (2.57)
Depression (PHQ-9, 0-27)			
Mean (SD)	5.00 (6.79)	3.14 (4.85)	6.65 (7.76)
Anxiety (GAD-7, 0-21)			
Mean (SD)	1.80 (3.02)	1.40 (2.66)	2.15 (3.27)
Neuroticism, 0-12			
Mean (SD)	3.25 (2.97)	2.80 (2.80)	3.64 (3.05)
Brain-fog (SSS)			
Mean (SD)	1.39 (0.570)	1.30 (0.491)	1.47 (0.622)
Fatigue Severity Scale (FSS)			
Mean (SD)	18.3 (13.0)	15.2 (10.5)	21.0 (14.3)
Doleur Neuropathique 4 (0-7)			
Mean (SD)	1.12 (1.36)	NA (NA)	1.12 (1.36)
Opioid use	1.12%	0.15%	1.98%
Tricyclic Antidepressant use	1.30%	0.53%	2.14%
Gabapentinoid use	0.85%	0.12%	1.49%

Supplementary Table B-3. Baseline characteristics of participants included in longitudinal analysis of FMI and executive function.

Higher values of Townsend Deprivation Index indicate greater social deprivation. Nociplastic pain assessed using the fibromyalgia index (FMI), with higher scores indicating more severe nociplastic pain. The FMI is the sum of the widespread pain index (WPI) and symptom severity scale (SSS). Pain intensity measured using numeric rating scale (NRS) among participants who indicated they had chronic pain, higher values indicate more severe pain. Depression measured using Patient Health Questionnaire 9-item on the pain questionnaire, with higher scores indicating more severe depression symptoms. Anxiety measured using the General Anxiety Disorder 7-item on the Mental Health and Well-being questionnaire, with higher scores indicating more severe anxiety symptoms. Brain-fog measured using item on subjective cognitive difficulties on SSS, with higher scores indicating more severe brai- fog symptoms. Fatigue measured using the Fatigue Severity Scale (FSS) on the pain questionnaire, with higher scores indicating more severe fatigue symptoms. Note this questionnaire was only offered to participants who reported fatigue on the SSS. Neuropathic pain symptoms measured using the Doleur Neuropathique 4 (DN4) on the pain questionnaire, with higher scores indicating more severe neuropathic symptoms. SD, standard deviation.

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		Included in longitudinal analysis		
	Total	**No**	**Yes**	**P-value**
	(N=35423)	(N=16525)	(N=18898)	
Sex				
Female	18588 (52 %)	8704 (53 %)	9884 (52 %)	0.796
Male	16835 (48 %)	7821 (47 %)	9014 (48 %)	
Age (years)				
Mean (SD)	64.5 (7.38)	64.4 (7.41)	64.5 (7.35)	0.136
Townsend Deprivation Index				
Mean (SD)	-1.90 (2.73)	-1.88 (2.76)	-1.91 (2.70)	0.72
Marital status				
Married/Partner	26540 (75 %)	12239 (74 %)	14301 (76 %)	0.0045
Not married	8746 (25 %)	4212 (25 %)	4534 (24 %)	
Employment status				
Employed	12567 (35 %)	5323 (32 %)	7244 (38 %)	<0.001
Retired	21544 (61 %)	10606 (64 %)	10938 (58 %)	
Unemployed/Other	1243 (4 %)	559 (3 %)	684 (4 %)	
White ethnicity, %	97.5%	97.3%	97.7%	0.0287
University degree, %	52.9%	51.6%	54.1%	<0.001
Current tobacco use, %	2.78%	2.80%	2.76%	0.982
Alcohol Use				
Never	2305 (7 %)	1145 (7 %)	1160 (6 %)	0.061
Rarely	7599 (21 %)	3592 (22 %)	4007 (21 %)	
Weekly	19409 (55 %)	8950 (54 %)	10459 (55 %)	
Daily	6033 (17 %)	2798 (17 %)	3235 (17 %)	
Body Mass Index (kg/m2)				
Mean (SD)	26.4 (4.46)	26.4 (4.50)	26.4 (4.43)	0.407
Fibromyalgia Index (0-31)				
Mean (SD)	3.59 (3.49)	3.67 (3.57)	3.52 (3.42)	<0.001
Widespread Pain Index (0-19)				
Mean (SD)	1.27 (1.97)	1.30 (2.03)	1.24 (1.91)	0.0195
Symptom Severity Scale (0-12)				
Mean (SD)	2.32 (2.09)	2.37 (2.11)	2.28 (2.07)	<0.001
Sleep duration, self reported				
Mean (SD)	7.16 (1.02)	7.16 (1.04)	7.16 (1.00)	0.98
Sleep duration, seld reported				
<7 hours	8261 (23 %)	3920 (24 %)	4341 (23 %)	0.0045
7-9 hours	24536 (69 %)	11296 (68 %)	13240 (70 %)	
>9 hours	2480 (7 %)	1237 (7 %)	1243 (7 %)	
Pain intensity, NRS (0-10)				
Mean (SD)	3.70 (2.58)	3.74 (2.59)	3.66 (2.57)	0.0797
Depression (PHQ-9, 0-27)				

		Included in longitudinal analysis		
	Total	**No**	**Yes**	**P-value**
Mean (SD)	5.19 (6.98)	5.41 (7.19)	5.00 (6.79)	<0.001
Anxiety (GAD-7, 0-21)				
Mean (SD)	1.80 (3.05)	1.79 (3.07)	1.80 (3.02)	0.989
Neuroticism, 0-12				
Mean (SD)	3.23 (2.96)	3.22 (2.96)	3.25 (2.97)	0.57
Brain-fog (SSS)				
Mean (SD)	1.39 (0.575)	1.40 (0.581)	1.39 (0.570)	0.12
Fatigue Severity Scale (FSS)				
Mean (SD)	18.6 (13.2)	18.9 (13.4)	18.3 (13.0)	<0.001
Doleur Neuropathique 4 (0-7)				
Mean (SD)	1.16 (1.39)	1.21 (1.43)	1.12 (1.36)	<0.001
Opioid use	1.13%	1.15%	1.12%	0.969
Tricyclic Antidepressant use	1.53%	1.70%	1.39%	0.0547
Gabapentinoid use	0.91%	0.98%	0.85%	0.411
Baseline executive function, Z				
Mean (SD)	0.00249 (0.999)	-0.0715 (1.08)	0.0672 (0.922)	<0.001

Supplementary Table B-4. Comparison of baseline characteristics of participants in cross-sectional analysis who also had follow-up cognitive outcome data available..

UK Biobank participants in cross-sectional analysis who did not have follow-up cognitive outcome data compared to those with follow-up cognitive outcome data. Comparisons between groups were made using ANOVA for continuous variables, and chi-square test for categorical variables. SD, standard deviation. Higher values of Townsend Deprivation Index indicate greater social deprivation. Nociplastic pain assessed using the fibromyalgia index (FMI), with higher scores indicating more severe nociplastic pain. The FMI is the sum of the widespread pain index (WPI) and symptom severity scale (SSS). Pain intensity measured using numeric rating scale (NRS) among participants who indicated they had chronic pain, higher values indicate more severe pain. Depression measured using Patient Health Questionnaire 9-item on the pain questionnaire, with higher scores indicating more severe depression symptoms. Anxiety measured using the General Anxiety Disorder 7-item on the Mental Health and Well-being questionnaire, with higher scores indicating more severe anxiety symptoms. Brain-fog measured using item on subjective cognitive difficulties on SSS, with higher scores indicating more severe brain-fog symptoms. Fatigue measured using the Fatigue Severity Scale (FSS) on the pain questionnaire, with higher scores indicating more severe fatigue symptoms. Note this questionnaire was only offered to participants who reported fatigue on the SSS. Neuropathic pain symptoms measured using the Doleur Neuropathique 4 (DN4) on the pain questionnaire, with higher scores indicating more severe neuropathic symptoms. Executive function derived from a latent variable at baseline, as described in the text.

B.3 Task performance

At both baseline and follow-up, participants with chronic pain at baseline consistently performed worse across the three cognitive tasks compared to those without chronic pain. On average, individuals with chronic pain scored 1 to 2 percentile ranks lower than those without chronic pain, indicating a modest but statistically significant difference in cognitive performance. There was a notable ceiling effect evident on the SDS.

Baseline					**Follow-up**				
	Total	**No Chronic pain**	**Chronic pain**	**P-value**		**Total**	**No Chronic pain**	**Chronic pain**	**P-value**
	(N=35423)	(N=16654)	(N=18769)			(N=18898)	(N=8876)	(N=10022)	
TMT, seconds					TMT, seconds				
Mean (SD)	34.3 (23.5)	34.0 (23.4)	34.6 (23.6)	0.0308	Mean (SD)	30.8 (19.1)	30.4 (20.4)	31.2 (18.0)	0.0186
TMT, centile rank					TMT, centile rank				
Mean (SD)	50.1 (28.8)	50.6 (28.9)	49.6 (28.8)	0.00504	Mean (SD)	50.1 (28.9)	50.9 (28.9)	49.4 (28.9)	0.00326
SDS, proportion correct					SDS, proportion correct				
Mean (SD)	0.954 (0.0934)	0.956 (0.0907)	0.952 (0.0957)	<0.001	Mean (SD)	0.964 (0.0858)	0.966 (0.0827)	0.963 (0.0885)	0.0193
SDS, centile rank					SDS, centile rank				
Mean (SD)	50.0 (28.8)	50.6 (28.6)	49.5 (29.1)	0.00149	Mean (SD)	50.0 (28.9)	50.5 (28.6)	49.6 (29.1)	0.0984
Matrix pattern test, proportion correct					Matrix pattern test, proportion correct				
Mean (SD)	0.597 (0.166)	0.604 (0.165)	0.590 (0.167)	<0.001	Mean (SD)	0.708 (0.181)	0.716 (0.180)	0.701 (0.182)	<0.001
Matrix pattern test, centile rank					Matrix pattern test, centile rank				
Mean (SD)	50.0 (28.9)	51.3 (28.8)	48.9 (28.9)	<0.001	Mean (SD)	50.0 (28.8)	51.3 (28.7)	48.9 (28.9)	<0.001

Supplementary Table B-5. Cognitive test scores at baseline and follow-up for participants with and without chronic pain. All results adjusted for age at the time of the test.

Comparisons between groups were conducted using two-sample t-tests. The TMT results indicate the difference in time taken to complete the alphanumeric and numeric courses, with higher values reflecting slower processing speed. SDS measures the proportion of correct responses, and the matrix pattern test assesses abstract reasoning accuracy. Chronic pain at baseline was consistently associated with lower performance, particularly on the TMT and matrix pattern test, highlighting a potential impact of chronic pain on executive function abilities. TMT, trail making test. SDS, digit-symbol substitution test. SD, standard deviation

B.4 Detailed regression results & diagnostics

B.4.1 Factor analysis

B.4.2 Cross-sectional analysis

	Model 1				Model 2			
Predictor	**Estimate**	**95% CI Lower**	**95% CI Upper**	**P**	**Estimate**	**95% CI Lower**	**95% CI Upper**	**P**
(Intercept)	-0.009	-0.032	0.013	0.401	-0.806	-0.874	-0.738	0.000
FMI:No Chronic pain	0.005	-0.003	0.013	0.213	0.007	0.000	0.015	0.054
FMI:Chronic pain	-0.027	-0.031	-0.023	0.000	-0.018	-0.021	-0.014	0.000
Chronic Pain	-0.033	-0.058	-0.008	0.010	-0.017	-0.041	0.007	0.156
Male sex	0.113	0.092	0.134	0.000	0.122	0.101	0.142	0.000
Age	-0.003	-0.005	-0.002	0.000	-0.003	-0.004	-0.001	0.000
University Degree					0.477	0.456	0.497	0.000
TDI					-0.018	-0.022	-0.014	0.000
White ethnicity					0.543	0.478	0.607	0.000
BMI					-0.007	-0.010	-0.005	0.000
Current Smoker					-0.105	-0.165	-0.044	0.001
poly(fup_cog0_eop, 2)1	-12.221	-14.169	-10.272	0.000	-11.373	-13.255	-9.491	0.000
poly(fup_cog0_eop, 2)2	3.475	1.524	5.427	0.000	3.170	1.282	5.058	0.001

Supplementary Table B-6. Cross-sectional relationship between fibromyalgia index (FMI) score and executive function, with chronic pain interaction.

Linear regression beta coefficients (Estimates), 95% confidence intervals (95% CI), and p-values are shown for two models predicting executive function (age-adjusted Z-score). The exposure of interest if the fibromyalgia index (FMI), which is a on a scale of 0 to 31. Model 1 adjusts for age, sex, and assessment order. Model 2 includes additional adjustments for sociodemographic factors (education level, Townsend deprivation index, ethnicity, body mass index, and smoking status). Interaction terms (e.g., FMI:Chronic pain) assess the moderating effect of chronic pain on the relationship between nociplastic pain severity and executive function. All continuous variables are mean-centred. `fup_cog0_eop` is the time in years between baseline cognitive assessment at the imaging visit, and response to the online pain questionnaire. Due to non-linearity, this was fitted with a polynomial term. The outcome is age-standardised executive function derived from confirmatory factor analysis with the Trail Making Test, Digit Symbol Substitution Test and Matrix Pattern Test (see methods section), and is on a standardised scale with a mean of 0 and standard deviation of 1.

	Model 1				Model 2			
Predictor	**Estimate**	**95% CI Lower**	**95% CI Upper**	**P**	**Estimate**	**95% CI Lower**	**95% CI Upper**	**P**
(Intercept)	49.61	48.97	50.25	0.000	27.98	26.02	29.94	0.000
FMI:No Chronic pain	0.17	-0.06	0.39	0.152	0.24	0.02	0.46	0.031
FMI:Chronic pain	-0.77	-0.87	-0.66	0.000	-0.49	-0.59	-0.39	0.000
Chronic Pain	-1.18	-1.90	-0.46	0.001	-0.70	-1.39	-0.01	0.048
Male sex	3.80	3.20	4.41	0.000	4.10	3.52	4.69	0.000
Age	0.03	-0.01	0.08	0.104	0.06	0.02	0.10	0.006
University Degree					14.31	13.72	14.89	0.000
TDI					-0.42	-0.53	-0.31	0.000
White ethnicity					13.96	12.10	15.82	0.000
BMI					-0.25	-0.31	-0.18	0.000
Current Smoker					-3.84	-5.59	-2.09	0.000
poly(fup_cog0_eop, 2)1	-415.34	-471.52	-359.16	0.000	-387.46	-441.61	-333.31	0.000
poly(fup_cog0_eop, 2)2	86.00	29.74	142.25	0.003	83.00	28.67	137.34	0.003

Supplementary Table B-7. Cross-sectional relationship between fibromyalgia index (FMI) score and executive function rank, with chronic pain interaction.

Linear regression beta coefficients (Estimates), 95% confidence intervals (95% CI), and p-values are shown for two models predicting executive function (age-adjusted centile rank). The exposure of interest if the fibromyalgia index (FMI), which is a on a scale of 0 to 31. Model 1 adjusts for age, sex, and assessment order. Model 2 includes additional adjustments for sociodemographic factors (education level, Townsend deprivation index, ethnicity, body mass index, and smoking status). Interaction terms (e.g., FMI:Chronic pain) assess the moderating effect of chronic pain on the relationship between nociplastic pain severity and executive function. All continuous variables are mean-centred. `fup_cog0_eop` is the time in years between baseline cognitive assessment at the imaging visit, and response to the online pain questionnaire. Due to non-linearity, this was fitted with a polynomial term. The outcome is age-standardised executive function centile rank derived from confirmatory factor analysis with the Trail Making Test, Digit Symbol Substitution Test and Matrix Pattern Test (see methods section).

	Model 1				Model 2			
Predictor	**Estimate**	**95% CI Lower**	**95% CI Upper**	**P**	**Estimate**	**95% CI Lower**	**95% CI Upper**	**P**
(Intercept)	0.057	0.037	0.076	0.000	-0.725	-0.792	-0.658	0.000
FMI:Female	-0.019	-0.023	-0.015	0.000	-0.011	-0.015	-0.007	0.000
FMI:Male	-0.026	-0.031	-0.021	0.000	-0.017	-0.022	-0.012	0.000
Chronic Pain	0.003	-0.020	0.026	0.786	0.011	-0.011	0.033	0.340
Male sex	-0.111	-0.132	-0.090	0.000	-0.120	-0.141	-0.100	0.000
Age	-0.003	-0.005	-0.002	0.000	-0.003	-0.004	-0.001	0.000
University Degree					0.478	0.458	0.498	0.000
TDI					-0.018	-0.022	-0.014	0.000
White ethnicity					0.546	0.482	0.611	0.000
BMI					-0.007	-0.010	-0.005	0.000
Current Smoker					-0.106	-0.167	-0.045	0.001
poly(fup_cog0_eop, 2)1	-12.265	-14.215	-10.316	0.000	-11.404	-13.287	-9.522	0.000
poly(fup_cog0_eop, 2)2	3.489	1.537	5.442	0.000	3.181	1.292	5.070	0.001

Supplementary Table B-8. Cross-sectional relationship between fibromyalgia index (FMI) score and executive function, with sex interaction.

Linear regression beta coefficients (Estimates), 95% confidence intervals (95% CI), and p-values are shown for two models predicting executive function (age-adjusted Z-score) among participants with chronic pain. The exposure of interest if the fibromyalgia index (FMI), which is a on a scale of 0 to 31. Model 1 adjusts for age, sex, and assessment order. Model 2 includes additional adjustments for sociodemographic factors (education level, Townsend deprivation index, ethnicity, body mass index, and smoking status). Interaction terms (e.g., FMI:Female) assess the moderating effect of chronic pain on the relationship between nociplastic pain severity and executive function. All continuous variables are mean-centred. ` fup_cog0_eop` is the time in years between baseline cognitive assessment at the imaging visit, and response to the online pain questionnaire. Due to non-linearity, this was fitted with a polynomial term. The outcome is age-standardised executive function derived from confirmatory factor analysis with the Trail Making Test, Digit Symbol Substitution Test and Matrix Pattern Test (see methods section), and is on a standardised scale with a mean of 0 and standard deviation of 1.

]

	Model 1				Model 2			
Predictor	**Estimate**	**95% CI Lower**	**95% CI Upper**	**P**	**Estimate**	**95% CI Lower**	**95% CI Upper**	**P**
(Intercept)	52.032	51.469	52.596	0.000	30.882	28.950	32.815	0.000
FMI:Female	-0.506	-0.622	-0.390	0.000	-0.278	-0.392	-0.165	0.000
FMI:Male	-0.772	-0.921	-0.623	0.000	-0.500	-0.644	-0.355	0.000
Chronic Pain	-0.129	-0.795	0.537	0.705	0.127	-0.515	0.769	0.699
Male sex	-3.725	-4.332	-3.118	0.000	-4.047	-4.638	-3.457	0.000
Age	0.028	-0.013	0.069	0.179	0.052	0.012	0.092	0.011
University Degree					14.336	13.753	14.918	0.000
TDI					-0.419	-0.526	-0.312	0.000
White ethnicity					14.060	12.199	15.920	0.000
BMI					-0.253	-0.320	-0.187	0.000
Current Smoker					-3.870	-5.625	-2.115	0.000
poly(fup_cog0_eop, 2)1	-416.527	-472.741	-360.312	0.000	-388.247	-442.422	-334.073	0.000
poly(fup_cog0_eop, 2)2	86.321	30.028	142.613	0.003	83.241	28.882	137.600	0.003

Supplementary Table B-9. Cross-sectional relationship between fibromyalgia index (FMI) score and executive function, with sex interaction.

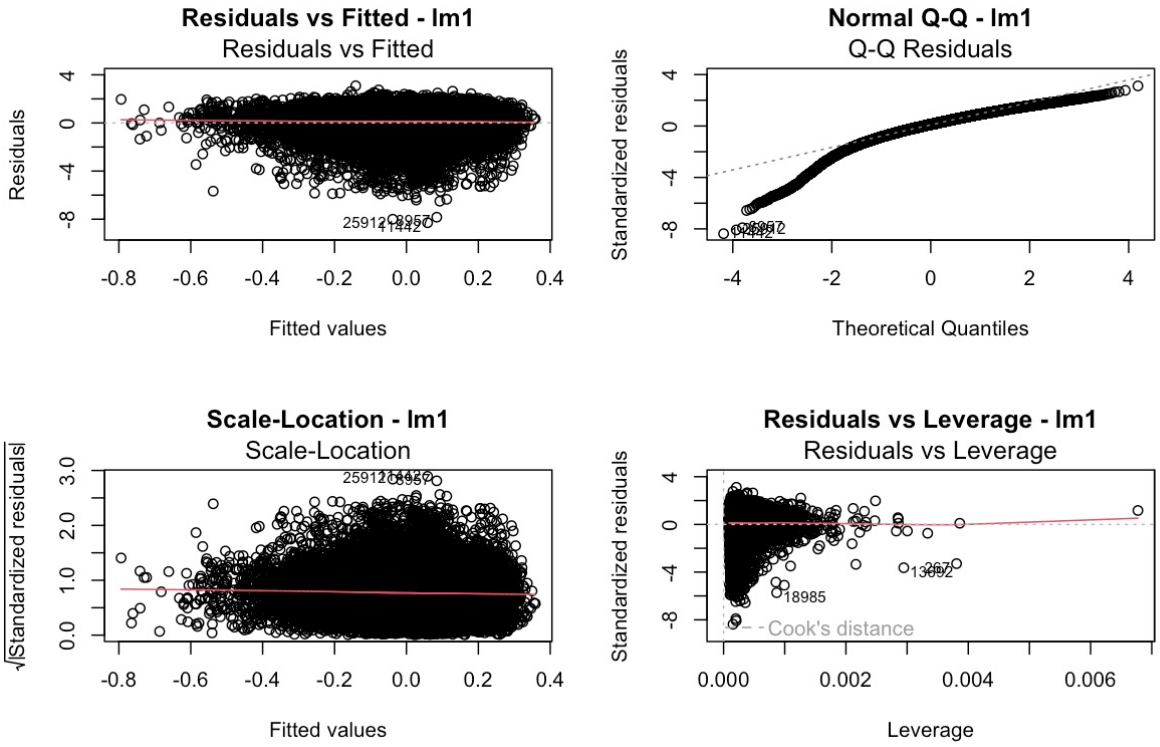
Linear regression beta coefficients (Estimates), 95% confidence intervals (95% CI), and p-values are shown for two models predicting executive function (age-adjusted centile rank) among participants with chronic pain. The exposure of interest if the fibromyalgia index (FMI), which is a on a scale of 0 to 31. Model 1 adjusts for age, sex, and assessment order. Model 2 includes additional adjustments for sociodemographic factors (education level, Townsend deprivation index, ethnicity, body mass index, and smoking status). Interaction terms (e.g., FMI:Female) assess the moderating effect of chronic pain on the relationship between nociplastic pain severity and executive function. All continuous variables are mean-centred. ` fup_cog0_eop` is the time in years between baseline cognitive assessment at the imaging visit, and response to the online pain questionnaire. Due to non-linearity, this was fitted with a polynomial term. The outcome is age-standardised executive function derived from confirmatory factor analysis with the Trail Making Test, Digit Symbol Substitution Test and Matrix Pattern Test (see methods section).

B.4.3 Model diagnostics

	GVIF	Df	GVIF^(1/(2*Df))
Chronic pain	1.45336921	1	1.20555763
Male sex	1.05426982	1	1.02677642
Baseline age	1.05984808	1	1.02948923
University degree	1.02786145	1	1.01383502
Townsend Deprivation Index (centred)	1.03277905	1	1.01625738
White ethnicity	1.01687251	1	1.00840097
Body Mass Index (centred)	1.06124767	1	1.03016876
Current smoker	1.0112869	1	1.00562762
poly(fup_cog0_eop, 2)	1.02213037	2	1.00548726
fmi_centered:cp_eop_bin	1.52822514	2	1.11185163

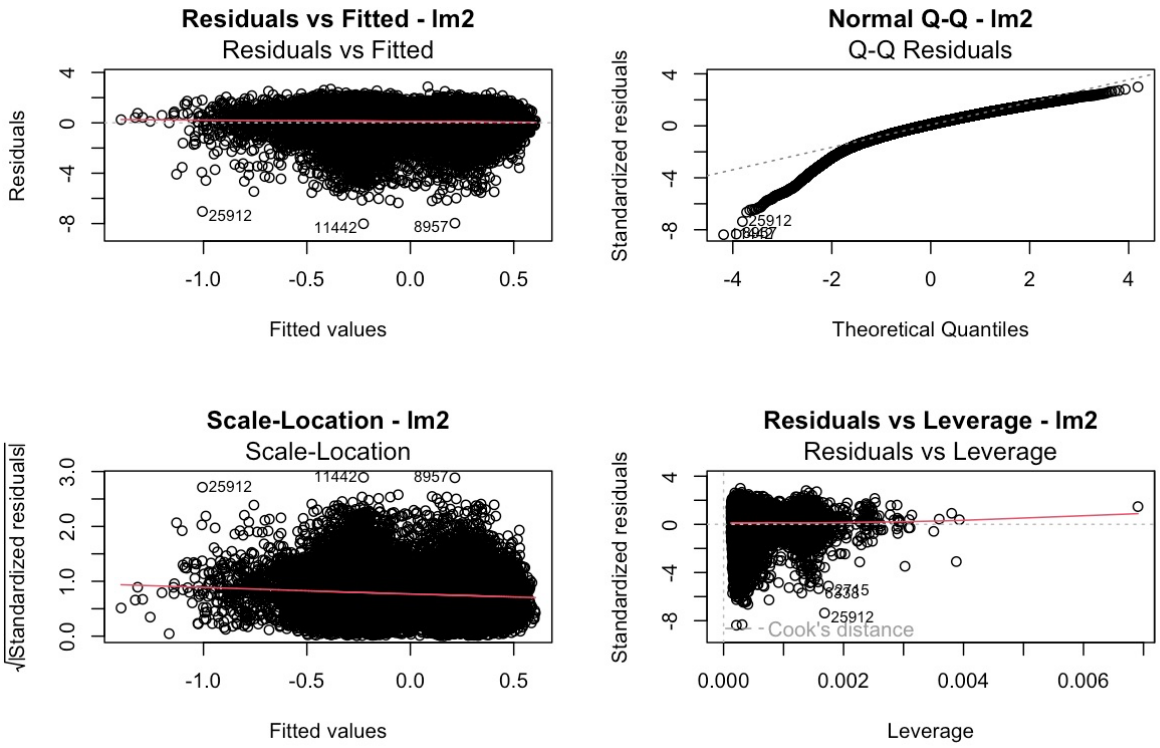
Supplementary Table B-10. No evidence of collinearity present in model.

GVIF used to account for variables with multiple degrees of freedom. GVIF, generalised variance inflation factor. Df, degrees of freedom.



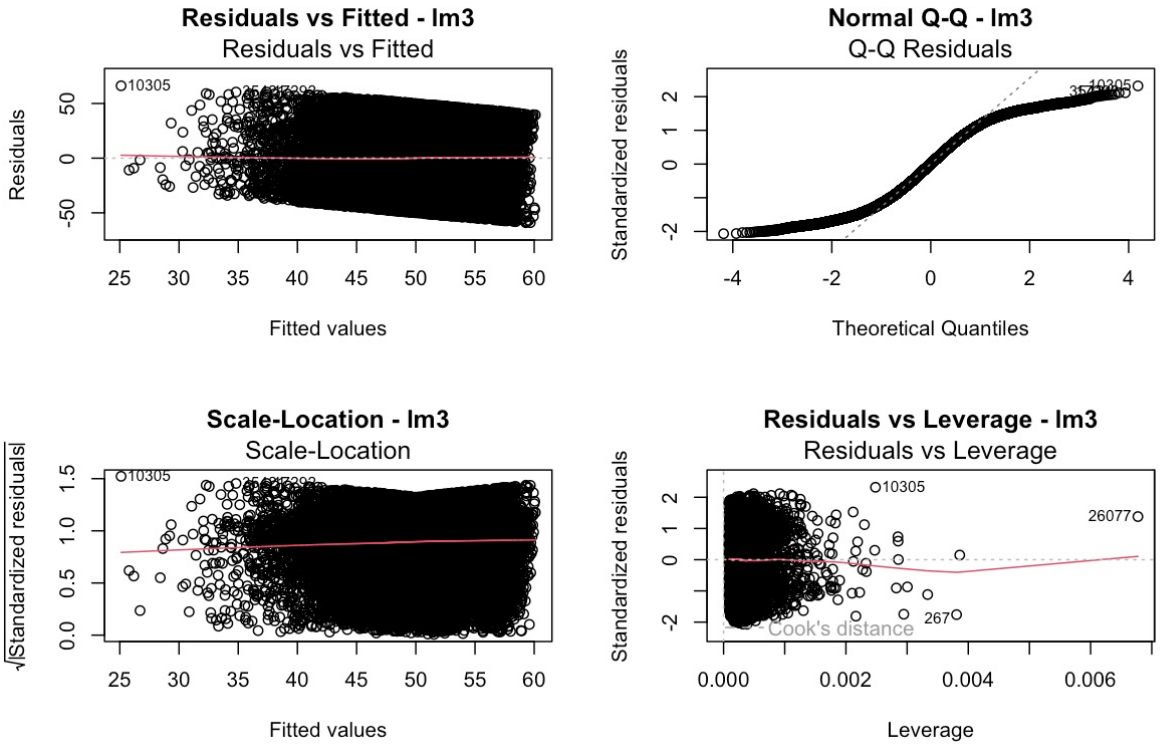
Supplementary Figure B-1. Diagnostic plots for linear regression analysis of FMI and baseline EF (minimally adjusted).

Diagnostic plots for models evaluating the relationship between fibromyalgia index (FMI) and executive function (Z-score), with interactions by chronic pain, adjusted for age, sex and assessment order. Each model shows: (1) residuals vs. fitted values plot to assess linearity, (2) Q-Q plot to examine residual normality, (3) scale-location plot to check homoscedasticity, and (4) residuals vs. leverage plot to identify influential points. Shaded regions represent 95% confidence intervals. Minor deviations from normality and slight heteroscedasticity in the rank-based models are noted, but these do not undermine model robustness due to the large sample size.



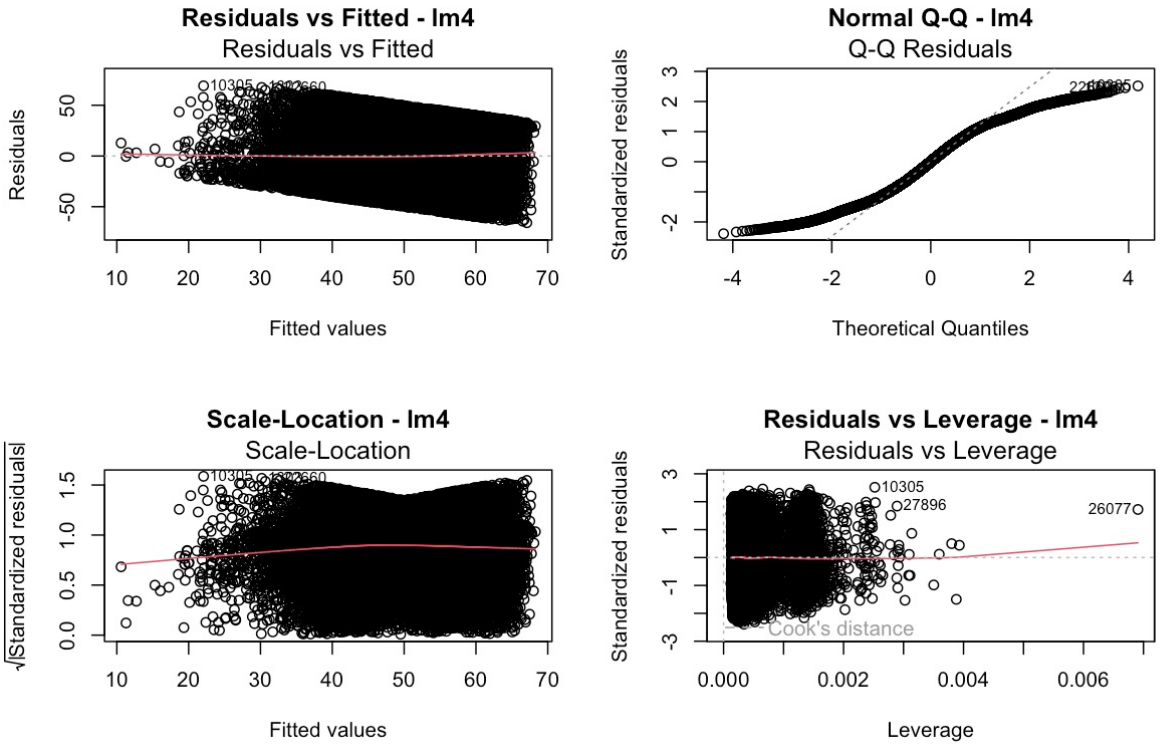
Supplementary Figure B-2. Diagnostic plots for linear regression analysis of FMI and baseline EF (fully adjusted model).

This figure presents diagnostic plots for the linear regression model investigating the relationship between baseline executive function and nociplastic pain severity (fibromyalgia index, FMI), moderated by chronic pain status and fully adjusted for sex, age, follow-up time (modelled as a quadratic term), education status (university degree, no degree), Townsend Deprivation Index, ethnicity (white, non-white), body mass index, and smoking status (current smoker, not current smoker). The ***Residuals vs. Fitted plot*** *reveals a degree of heteroscedasticity, as indicated by the non-random distribution of residuals. The* ***Q-Q plot*** *shows some deviations from normality in the residuals, particularly in the negative tail. The* ***Scale-Location plot*** *suggests a degree heteroscedasticity, with standardised residuals exhibiting some uneven spread across fitted values. The* ***Residuals vs. Leverage plot*** *identifies potential influential observations with high leverage, as indicated by points approaching or exceeding Cook's distance thresholds.*



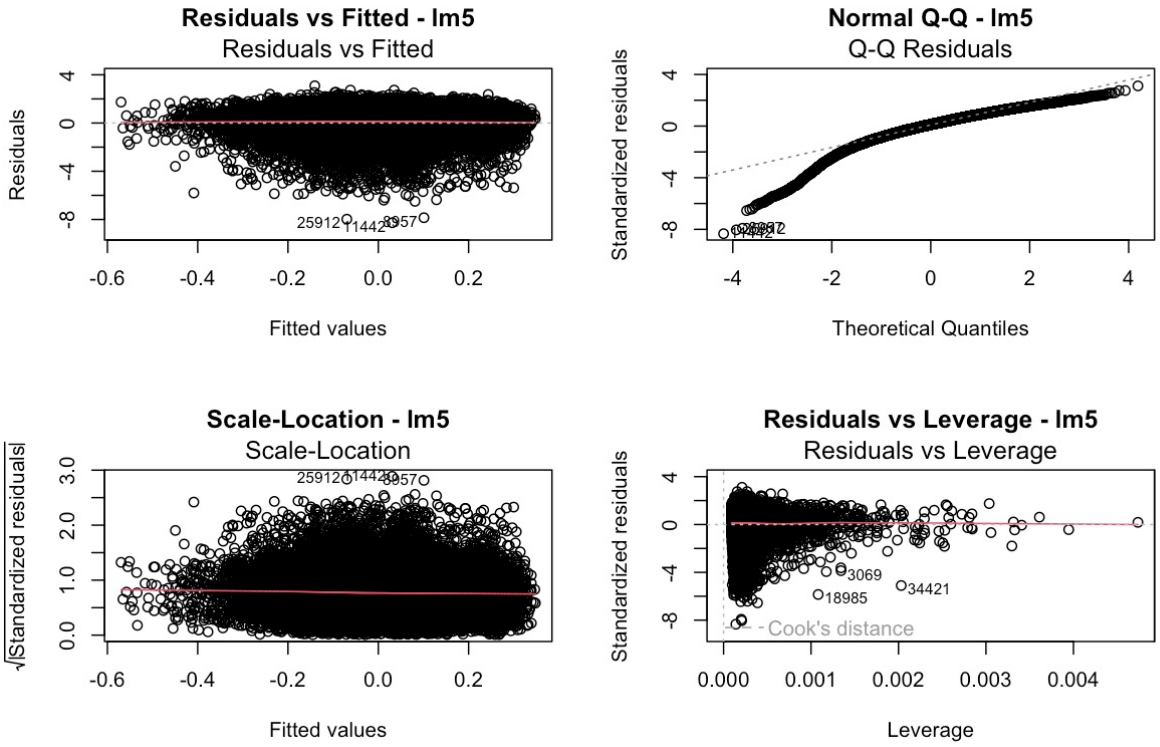
Supplementary Figure B-3. Diagnostic plots for linear regression analysis of FMI and baseline EF centile rank (minimally adjusted model).

*This figure presents diagnostic plots for the linear regression model investigating the relationship between baseline executive function and nociplastic pain severity (fibromyalgia index, FMI), moderated by chronic pain status and adjusted for sex, age, and follow-up time (modelled as a quadratic term). The **Residuals vs. Fitted plot** reveals a degree of heteroscedasticity, as indicated by the non-random distribution of residuals. The **Q-Q plot** shows some deviations from normality in the residuals, particularly in the negative tail. The **Scale-Location plot** suggests a degree heteroscedasticity, with standardised residuals exhibiting some uneven spread across fitted values. The **Residuals vs. Leverage plot** identifies potential influential observations with high leverage, as indicated by points approaching or exceeding Cook's distance thresholds.*



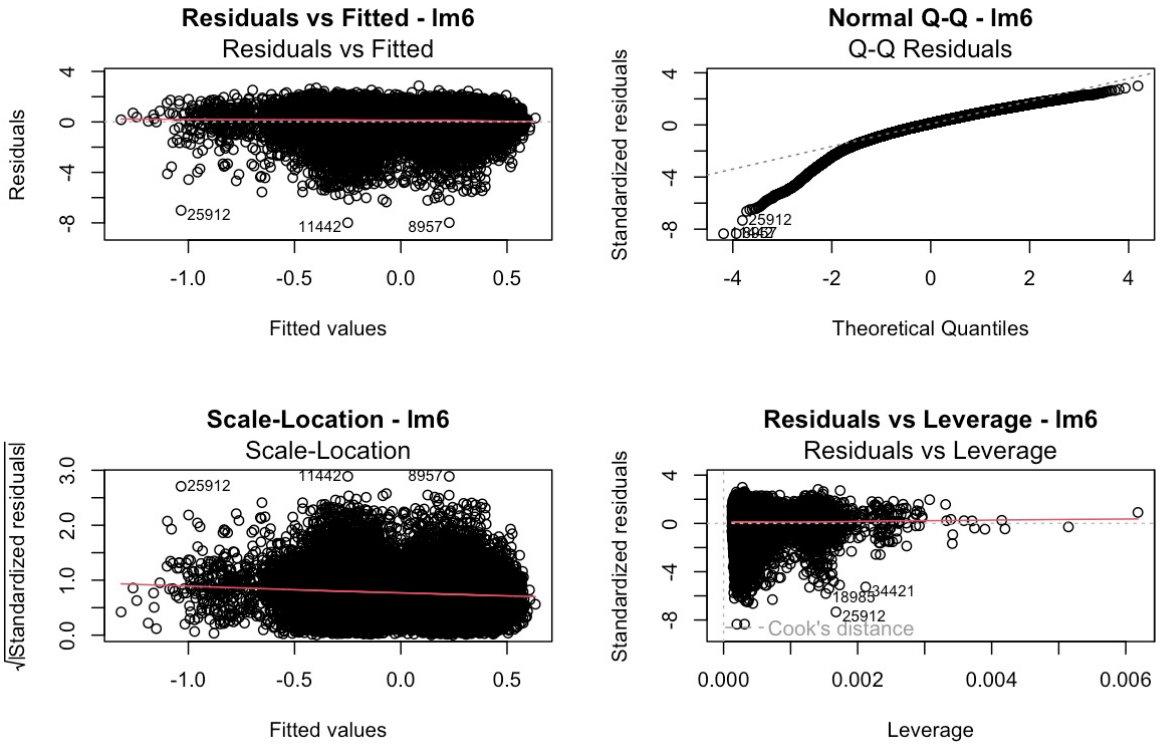
Supplementary Figure B-4. Diagnostic plots for linear regression analysis of FMI and baseline EF centile rank (fully adjusted model).

*This figure presents diagnostic plots for the linear regression model investigating the relationship between baseline executive function and nociplastic pain severity (fibromyalgia index, FMI), moderated by chronic pain status and fully adjusted for sex, age, follow-up time (modelled as a quadratic term), education status (university degree, no degree), Townsend Deprivation Index, ethnicity (white, non-white), body mass index, and smoking status (current smoker, not current smoker). The **Residuals vs. Fitted plot** reveals a degree of heteroscedasticity, as indicated by the non-random distribution of residuals. The **Q-Q plot** shows some deviations from normality in the residuals, particularly in the negative tail. The **Scale-Location plot** suggests a degree heteroscedasticity, with standardised residuals exhibiting some uneven spread across fitted values. The **Residuals vs. Leverage plot** identifies potential influential observations with high leverage, as indicated by points approaching or exceeding Cook's distance thresholds.*



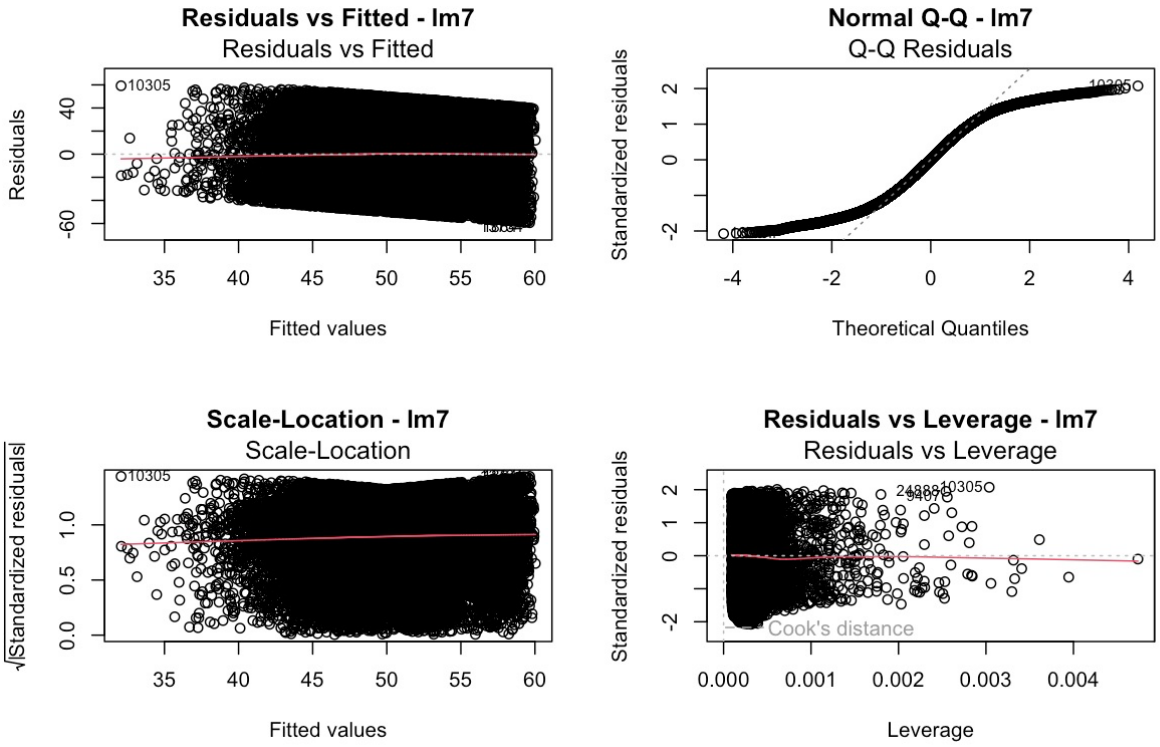
Supplementary Figure B-5. Diagnostic plots for linear regression analysis of FMI and baseline EF (stratified by sex, minimally adjusted).

*This figure presents diagnostic plots for the linear regression model investigating the relationship between baseline executive function and nociplastic pain severity (fibromyalgia index, FMI) in participants with chronic pain, moderated by sex, and adjusted for sex, and follow-up time (modelled as a quadratic term). The **Residuals vs. Fitted plot** reveals a degree of heteroscedasticity, as indicated by the non-random distribution of residuals. The **Q-Q plot** shows some deviations from normality in the residuals, particularly in the negative tail. The **Scale-Location plot** suggests a degree heteroscedasticity, with standardised residuals exhibiting some uneven spread across fitted values. The **Residuals vs. Leverage plot** identifies potential influential observations with high leverage, as indicated by points approaching or exceeding Cook's distance thresholds.*



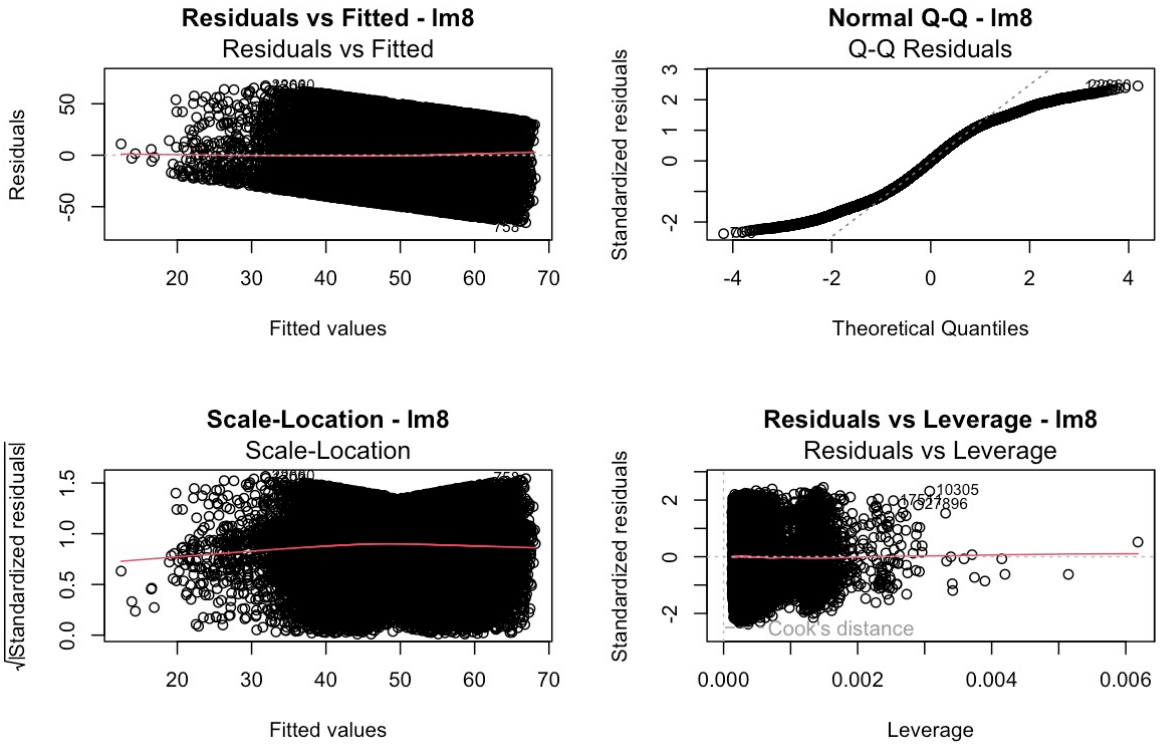
Supplementary Figure B-6. Diagnostic plots for linear regression analysis of FMI and baseline EF (stratified by sex, fully adjusted).

*This figure presents diagnostic plots for the linear regression model investigating the relationship between baseline executive function and nociplastic pain severity (fibromyalgia index, FMI) in participants with chronic pain, moderated by sex, and fully adjusted for sex, follow-up time (modelled as a quadratic term), education status (university degree, no degree), Townsend Deprivation Index, ethnicity (white, non-white), body mass index, and smoking status (current smoker, not current smoker). The **Residuals vs. Fitted plot** reveals a degree of heteroscedasticity, as indicated by the non-random distribution of residuals. The **Q-Q plot** shows some deviations from normality in the residuals, particularly in the negative tail. The **Scale-Location plot** suggests a degree heteroscedasticity, with standardised residuals exhibiting some uneven spread across fitted values. The **Residuals vs. Leverage plot** identifies potential influential observations with high leverage, as indicated by points approaching or exceeding Cook's distance thresholds.*



Supplementary Figure B-7. Diagnostic plots for linear regression analysis of FMI and baseline EF centile rank (stratified by sex, minimally adjusted).

*This figure presents diagnostic plots for the linear regression model investigating the relationship between baseline executive function centile rank and nociplastic pain severity (fibromyalgia index, FMI) in participants with chronic pain, moderated by sex, and adjusted for sex, and follow-up time (modelled as a quadratic term). The **Residuals vs. Fitted plot** reveals a degree of heteroscedasticity, as indicated by the non-random distribution of residuals. The **Q-Q plot** shows some deviations from normality in the residuals, particularly in the negative tail. The **Scale-Location plot** suggests a degree heteroscedasticity, with standardised residuals exhibiting some uneven spread across fitted values. The **Residuals vs. Leverage plot** identifies potential influential observations with high leverage, as indicated by points approaching or exceeding Cook's distance thresholds.*



Supplementary Figure B-8. Diagnostic plots for linear regression analysis of FMI and baseline EF centile rank (stratified by sex, fully adjusted).

*This figure presents diagnostic plots for the linear regression model investigating the relationship between baseline executive function centile rank and nociplastic pain severity (fibromyalgia index, FMI) in participants with chronic pain, moderated by sex, and fully adjusted for sex, follow-up time (modelled as a quadratic term), education status (university degree, no degree), Townsend Deprivation Index, ethnicity (white, non-white), body mass index, and smoking status (current smoker, not current smoker). The **Residuals vs. Fitted plot** reveals a degree of heteroscedasticity, as indicated by the non-random distribution of residuals. The **Q-Q plot** shows some deviations from normality in the residuals, particularly in the negative tail. The **Scale-Location plot** suggests a degree heteroscedasticity, with standardised residuals exhibiting some uneven spread across fitted values. The **Residuals vs. Leverage plot** identifies potential influential observations with high leverage, as indicated by points approaching or exceeding Cook's distance thresholds.*

B.5 Longitudinal CFA

1.1.1

Path	Predictor	Estimate	SE	z-value	p-value	CI Lower	CI Upper
Unadjusted							
EF_fup	FMI	-0.043	0.017	-2.578	0.0099	-0.075	-0.010
EF_base	FMI	-0.208	0.019	-11.134	0.0000	-0.245	-0.172
indirect (via EF_base)	a1*b1	-0.153	0.015	-10.455	0.0000	-0.182	-0.125
direct	c0	-0.043	0.017	-2.578	0.0099	-0.075	-0.010
total	a1*b1+c0	-0.196	0.017	-11.599	0.0000	-0.229	-0.163
Minimally adjusted							
EF_fup	FMI	-0.042	0.017	-2.536	0.0112	-0.074	-0.010
EF_base	FMI	-0.191	0.019	-10.086	0.0000	-0.228	-0.154
indirect (via EF_base)	a1*b1	-0.141	0.015	-9.556	0.0000	-0.170	-0.112
direct	c0	-0.042	0.017	-2.536	0.0112	-0.074	-0.010
total	direct+indirect	-0.183	0.017	-10.549	0.0000	-0.217	-0.149
Fully adjusted							
EF_fup	FMI	-0.021	0.017	-1.212	0.2255	-0.055	0.013
EF_base	FMI	-0.110	0.016	-6.734	0.0000	-0.142	-0.078
indirect (via EF_base)	a1*b1	-0.107	0.017	-6.417	0.0000	-0.140	-0.074
direct	c0	-0.021	0.017	-1.212	0.2255	-0.055	0.013
total	indirect+direct	-0.128	0.018	-7.165	0.0000	-0.163	-0.093

Supplementary Table B-11 Longitudinal SEM analysis of the indirect and direct effects of nociplastic pain severity (FMI) on executive function.

This table presents standardised parameter estimates, 95% confidence intervals (CI), standard errors (SE), z-values, and p-values for indirect pathways (via baseline EF), the total effect, and the direct effect of FMI on follow-up EF. Negative estimates indicate associations with lower executive function scores. EF_base, baseline executive function. EF_fup, follow-up executive function. FMI, fibromyalgia index.

B.6 Mediation analyses

Path	Predictor	Estimate	SE	z-value	p-value	CI Lower	CI Upper
EF_fup	FMI	0.009	0.021	0.446	0.65545	-0.032	0.051
EF_base	FMI	-0.082	0.027	-3.017	0.00255	-0.136	-0.029
cog	a0*b0	-0.064	0.021	-2.977	0.00291	-0.106	-0.022
sleep1	a1*b1	0.001	0.002	0.526	0.59865	-0.003	0.006
pain1	a2*b2	0.000	0.005	0.078	0.93803	-0.010	0.011
depression1	a3*b3	-0.005	0.012	-0.371	0.71086	-0.029	0.020
anxiety1	a4*b4	-0.010	0.005	-1.824	0.06817	-0.020	0.001
brainfog1	a5*b5	-0.006	0.011	-0.527	0.59799	-0.027	0.016
fatigue1	a6*b6	-0.018	0.013	-1.401	0.16126	-0.043	0.007
total1	c0+cog+sleep1+pain1+depression1+anxiety1+brainfog1+fatigue1	-0.091	0.023	-3.948	0.00008	-0.136	-0.046
space1	sleep1+pain1+depression1+anxiety1+brainfog1+fatigue1	-0.036	0.015	-2.350	0.01878	-0.067	-0.006
direct1	c0	0.009	0.021	0.446	0.65545	-0.032	0.051
sleep0	a1*e1	-0.013	0.003	-4.580	0.00000	-0.019	-0.008
pain0	a2*e2	-0.030	0.006	-5.112	0.00000	-0.042	-0.019
depression0	a3*e3	0.045	0.015	2.952	0.00316	0.015	0.074
anxiety0	a4*e4	-0.030	0.007	-4.253	0.00002	-0.043	-0.016
brainfog0	a5*e5	-0.004	0.014	-0.321	0.74830	-0.031	0.022
fatigue0	a6*e6	-0.004	0.016	-0.238	0.81200	-0.036	0.028
total0	a0+sleep0+pain0+depression0+anxiety0+brainfog0+fatigue0	-0.119	0.017	-6.836	0.00000	-0.154	-0.085
space0	sleep0+pain0+depression0+anxiety0+brainfog0+fatigue0	-0.037	0.020	-1.811	0.07015	-0.077	0.003
direct0	a0	-0.082	0.027	-3.017	0.00255	-0.136	-0.029

Supplementary Table B-12. Mediation analysis of the indirect and direct effects of SPACE symptom domains on the association between Fibromyalgia Index (FMI) score and executive function.

This table presents standardised parameter estimates, 95% confidence intervals (CI), standard errors (SE), z-values, and p-values for indirect pathways (baseline EF [cog], sleep, pain, depression, anxiety, brain-fog, and fatigue), the total effect, the combined indirect effect of all SPACE symptoms, and the direct effect of FMI on EF. Negative estimates indicate associations with lower executive function scores. Indirect effects on follow-up EF are indicated by paths annotated by "1", while those on baseline EF are indicated by "0". EF_base, baseline executive function. EF_fup, follow-up executive function. FMI, fibromyalgia index.

Path	Predictor	Estimate	SE	z-value	p-value	CI Lower	CI Upper
EF_fup	fmi.z	-0.038	0.029	-1.305	0.19198	-0.096	0.019
EF_base	fmi.z	-0.128	0.034	-3.711	0.00021	-0.195	-0.060
cog	a0*b0	-0.099	0.027	-3.683	0.00023	-0.152	-0.046
pain1	a1*b1	0.001	0.005	0.170	0.86476	-0.010	0.011
wpi1	a2*b2	0.018	0.024	0.742	0.45811	-0.029	0.065
neuropathic1	a3*b3	-0.008	0.005	-1.433	0.15182	-0.018	0.003
total1	c0+cog+pain1+wpi1+neuropathic1	-0.126	0.028	-4.471	0.00001	-0.181	-0.071
indirect1	pain1+wpi1+neuropathic1	0.011	0.024	0.451	0.65201	-0.037	0.059
direct1	c0	-0.038	0.029	-1.305	0.19198	-0.096	0.019
pain0	a1*e1	-0.027	0.006	-4.192	0.00003	-0.039	-0.014
wpi0	a2*e2	0.069	0.029	2.381	0.01728	0.012	0.126
neuropathic0	a3*e3	-0.034	0.007	-5.109	0.00000	-0.047	-0.021
total0	a0+pain0+wpi0+neuropathic0	-0.120	0.018	-6.776	0.00000	-0.154	-0.085
indirect0	pain0+wpi0+neuropathic0	0.008	0.030	0.273	0.78507	-0.050	0.066
direct0	a0	-0.128	0.034	-3.711	0.00021	-0.195	-0.060

Supplementary Table B-13. Mediation analysis of the indirect and direct effects of pain characteristics on the association between Fibromyalgia Index (FMI) score and executive function.

This table presents standardised parameter estimates, 95% confidence intervals (CI), standard errors (SE), z-values, and p-values for indirect pathways (baseline EF [cog], pain severity, widespread pain [wpi], and neuropathic pain), the total effect, the combined indirect effect of all pain characteristics, and the direct effect of FMI on EF. Negative estimates indicate associations with lower executive function scores. Indirect effects on follow-up EF are indicated by paths annotated by "1", while those on baseline EF are indicated by "0". EF_base, baseline executive function. EF_fup, follow-up executive function. FMI, fibromyalgia index.

Path	Predictor	Estimate	SE	z-value	p-value	CI Lower	CI Upper
EF_fup	FMI	-0.032	0.016	-2.026	0.04276	-0.064	-0.001
EF_base	FMI	-0.112	0.018	-6.178	0.00000	-0.147	-0.076
cog	a0*b0	-0.087	0.014	-6.041	0.00000	-0.115	-0.059
opioid1	a1*b1	0.003	0.002	1.481	0.13853	-0.001	0.007
tca1	a2*b2	0.002	0.002	1.335	0.18172	-0.001	0.005
gaba1	a3*b3	0.000	0.002	-0.002	0.99878	-0.004	0.004
total1	c0+cog+opioid1+tca1+gaba1	-0.114	0.017	-6.618	0.00000	-0.148	-0.080
indirect1	opioid1+tca1+gaba1	0.005	0.003	1.758	0.07869	-0.001	0.011
direct1	c0	-0.032	0.016	-2.026	0.04276	-0.064	-0.001
opioid0	a1*e1	-0.002	0.003	-0.707	0.47953	-0.007	0.003
tca0	a2*e2	-0.004	0.002	-2.011	0.04437	-0.008	0.000
gaba0	a3*e3	-0.003	0.002	-1.008	0.31341	-0.007	0.002
total0	a0+opioid0+tca0+gaba0	-0.120	0.018	-6.779	0.00000	-0.155	-0.085
indirect0	opioid0+tca0+gaba0	-0.008	0.004	-2.187	0.02874	-0.016	-0.001
direct0	a0	-0.112	0.018	-6.178	0.00000	-0.147	-0.076

Supplementary Table B-14. Mediation analysis of the indirect and direct effects of self-reported analgesia use on the association between Fibromyalgia Index (FMI) score and executive function.

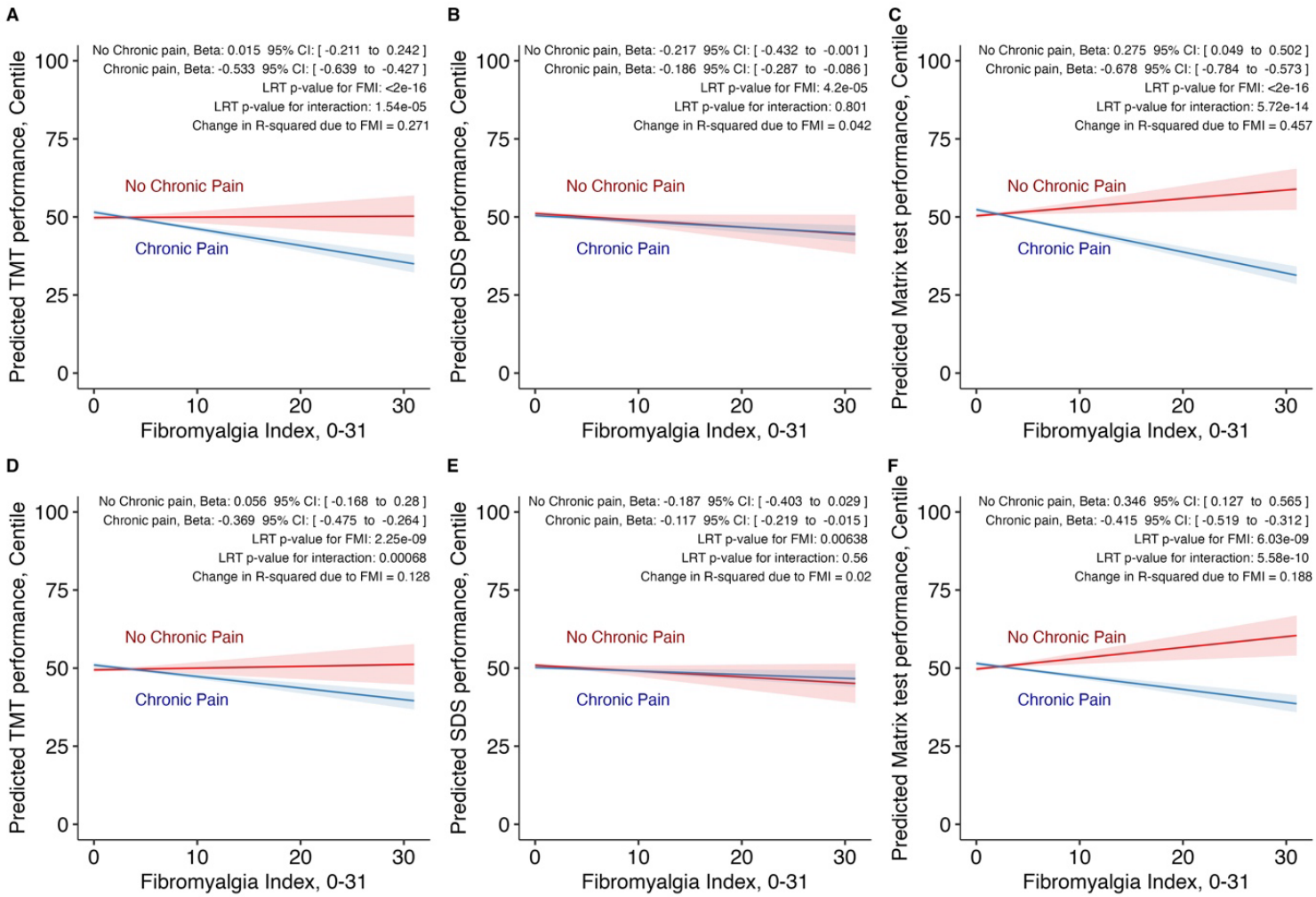
This table presents standardised parameter estimates, 95% confidence intervals (CI), standard errors (SE), z-values, and p-values for indirect pathways (baseline EF [cog], self-reported opioid, tricyclic antidepressant [tca], and gabapentinoid [gaba] use), the total effect, the combined indirect effect of all analgesia use, and the direct effect of FMI on EF. Negative estimates indicate associations with lower executive function scores. Indirect effects on follow-up EF are indicated by paths annotated by "1", while those on baseline EF are indicated by "0". EF_base, baseline executive function. EF_fup, follow-up executive function. FMI, fibromyalgia index.

B.7 Sensitivity analyses

B.7.1 Individual cognitive tests

B.7.1.1 Individual cognitive tests

Higher FMI scores were associated with poorer performance on each of the three cognitive tasks among participants with chronic pain, with a significant interaction with chronic pain for the TMT and Matrix pattern test (). The strongest effect was seen with the Matrix pattern test (**C&F**), and weakest with the SDS (**B&E**), perhaps reflecting the ceiling effect observed in this latter task. Detailed results are given in Supplementary Table B-15 to Supplementary Table B-17.



Supplementary Figure B-9. Higher fibromyalgia index (FMI) associated with worse performance on all three tests of executive function in adults with chronic pain.

Panels display predicted cognitive performance scores in centiles for trail-making test (TMT, panels A and D), digit-symbol substitution (SDS, panels B and E), and matrix pattern recognition (Matrix, panels C and F) across FMI scores for participants with and without chronic pain. Panels A, B, and C are adjusted for age, sex, and assessment order, while panels D, E, and F include further adjustments for ethnicity, socioeconomic status, education, body mass index (BMI), and tobacco use. Shaded regions represent 95% confidence intervals. A stronger negative association between FMI and cognitive performance is evident in participants with chronic pain across the TMT and Matrix tasks, as indicated by significant interaction P-values. This suggests that increasing FMI scores are associated with reduced cognitive function specifically among individuals with chronic pain.

	Estimate	Std. Error	t value	Pr(>|t|)
Minimally-adjusted model				
(Intercept)	49.537	0.326	152.036	0
Chronic Pain	-1.429	0.367	-3.896	0.0001
Male Sex	4.171	0.31	13.465	0
Baseline Age	-0.101	0.021	-4.796	0
poly(fup_cog0_eop, 2)1	-295.429	28.715	-10.288	0
poly(fup_cog0_eop, 2)2	25.926	28.755	0.902	0.36727
FMI:No Chronic pain	0.275	0.116	2.383	0.01719
FMI:Chronic pain	-0.678	0.054	-12.561	0
Fully-adjusted model				
	Estimate	**Std. Error**	**t value**	**Pr(>|t|)**
(Intercept)	29.547	1.005	29.4	0
Chronic Pain	-0.967	0.355	-2.724	0.00645
Male Sex	4.437	0.302	14.682	0
Baseline Age	-0.074	0.021	-3.613	0.0003
University Degree	13.891	0.299	46.53	0
TDI	-0.365	0.055	-6.679	0
White ethnicity	12.493	0.954	13.097	0
BMI	-0.234	0.034	-6.892	0
Current smoker	-2.488	0.899	-2.766	0.00567
poly(fup_cog0_eop, 2)1	-268.606	27.769	-9.673	0
poly(fup_cog0_eop, 2)2	25.297	27.863	0.908	0.36394
FMI:No Chronic pain	0.346	0.112	3.092	0.00199
FMI:Chronic pain	-0.415	0.053	-7.856	0

Supplementary Table B-15. Cross-sectional relationship between fibromyalgia index (FMI) score and Matrix Pattern test score, with interaction with chronic pain.

Linear regression beta coefficients (Estimates), 95% confidence intervals (95% CI), and p-values are shown for two models predicting matrix pattern test (centile rank, where higher values indicate better performance) with an interaction with chronic pain. The exposure of interest is the fibromyalgia index (FMI), which is mean centred and a on a scale of 0 to 31. Model 1 adjusts for age, sex, and assessment order. Model 2 includes additional adjustments for sociodemographic factors (education level, Townsend deprivation index, ethnicity, body mass index, and smoking status). Interaction terms (e.g., FMI:Chronic Pain) assess the moderating effect of chronic pain on the relationship between nociplastic pain severity and matrix pattern test. All continuous variables are mean-centred.
`fup_cog0_eop` is the time in years between baseline cognitive assessment at the imaging visit, and response to the online pain questionnaire. Due to non-linearity, this was fitted with a polynomial term.

	Estimate	Std. Error	t value	Pr(>|t|)
Minimally-adjusted model				
(Intercept)	50.247	0.326	154.239	0.00000
Chronic Pain	-0.235	0.367	-0.641	0.52183
Male Sex	0.823	0.310	2.658	0.00787
Baseline Age	0.324	0.021	15.461	0.00000
poly(fup_cog0_eop, 2)1	-377.245	28.711	-13.139	0.00000
poly(fup_cog0_eop, 2)2	119.387	28.750	4.153	0.00003
fmi_centered:cp_eop_binNo Chronic pain	0.015	0.116	0.132	0.89502
fmi_centered:cp_eop_binChronic pain	-0.533	0.054	-9.875	0.00000
Fully-adjusted model				
(Intercept)	35.852	1.026	34.957	0.00000
Chronic Pain	0.015	0.362	0.042	0.96620
Male Sex	0.948	0.308	3.075	0.00211
Baseline Age	0.331	0.021	15.821	0.00000
University Degree	8.613	0.305	28.270	0.00000
TDI	-0.363	0.056	-6.507	0.00000
White ethnicity	9.901	0.973	10.171	0.00000
BMI	-0.084	0.035	-2.413	0.01583
Current smoker	-3.904	0.918	-4.254	0.00002
poly(fup_cog0_eop, 2)1	-361.493	28.338	-12.756	0.00000
poly(fup_cog0_eop, 2)2	112.066	28.434	3.941	0.00008
FMI:No Chronic pain	0.056	0.114	0.491	0.62328
FMI:Chronic pain	-0.369	0.054	-6.848	0.00000

Supplementary Table B-16. Cross-sectional relationship between fibromyalgia index (FMI) score and Trail Making Test score, with interaction with chronic pain.

Linear regression beta coefficients (Estimates), 95% confidence intervals (95% CI), and p-values are shown for two models predicting Trail Making Test performance (centile rank, where higher values indicate better performance) with an interaction with chronic pain. The exposure of interest is the fibromyalgia index (FMI), which is mean centred and a on a scale of 0 to 31. Model 1 adjusts for age, sex, and assessment order. Model 2 includes additional adjustments for sociodemographic factors (education level, Townsend deprivation index, ethnicity, body mass index, and smoking status). Interaction terms (e.g., FMI:Chronic Pain) assess the moderating effect of chronic pain on the relationship between nociplastic pain severity and Trail Making test. All continuous variables are mean-centred. `fup_cog0_eop` is the time in years between baseline cognitive assessment at the imaging visit, and response to the online pain questionnaire. Due to non-linearity, this was fitted with a polynomial term.

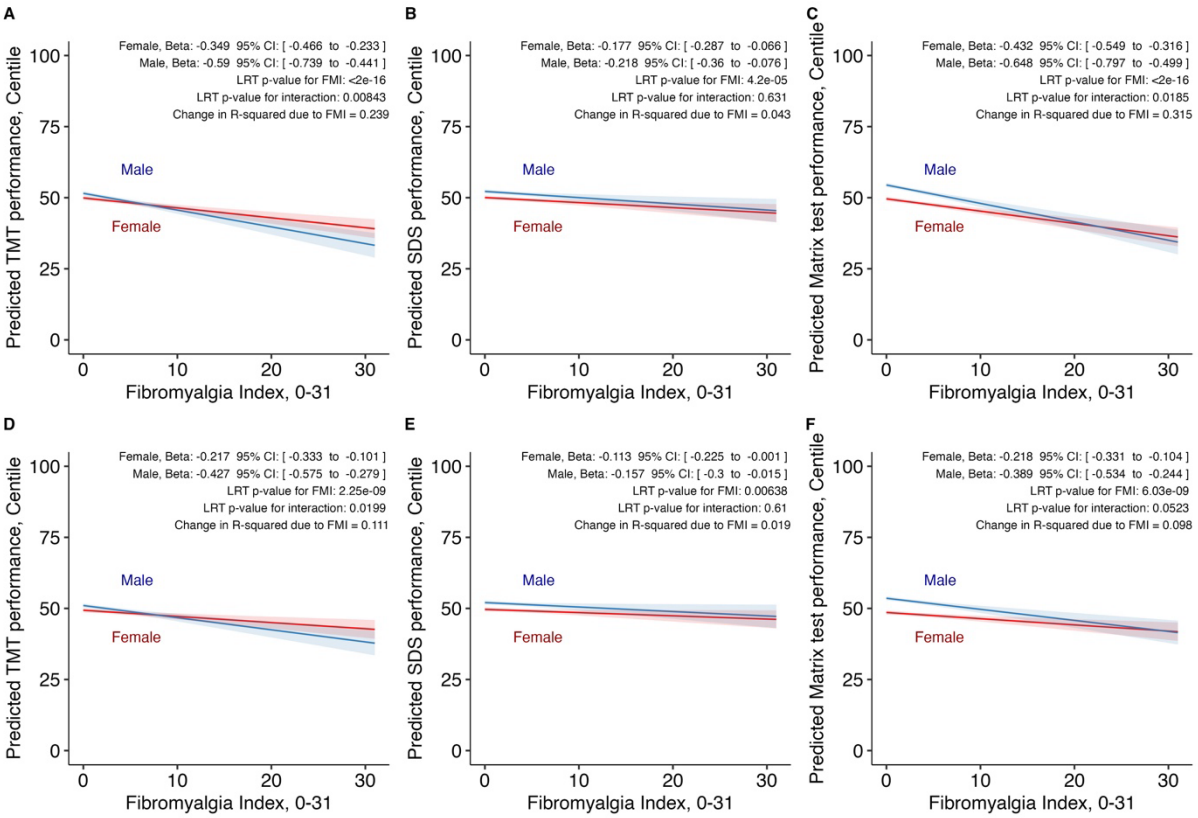
	Estimate	Std. Error	t value	Pr(>|t|)
Minimally-adjusted model				
(Intercept)	49.324	0.31	159.104	0
Chronic Pain	-0.559	0.349	-1.601	0.10934
Male Sex	2.025	0.295	6.871	0
Baseline Age	1.221	0.02	61.149	0
poly(fup_cog0_eop, 2)1	-528.573	27.322	-19.346	0
poly(fup_cog0_eop, 2)2	-8.021	27.359	-0.293	0.76939
FMI:No Chronic pain	-0.217	0.11	-1.971	0.0487
FMI:Chronic pain	-0.186	0.051	-3.627	0.00029
Fully-adjusted model				
(Intercept)	44.62	0.988	45.148	0
Chronic Pain	-0.416	0.349	-1.192	0.23333
Male Sex	2.248	0.297	7.564	0
Baseline Age	1.218	0.02	60.397	0
University Degree	1.76	0.294	5.995	0
TDI	-0.063	0.054	-1.167	0.24341
White ethnicity	3.655	0.938	3.896	0.0001
BMI	-0.191	0.033	-5.74	0
Current smoker	-0.204	0.884	-0.231	0.81755
poly(fup_cog0_eop, 2)1	-524.124	27.307	-19.194	0
poly(fup_cog0_eop, 2)2	-9.236	27.4	-0.337	0.73605
FMI:No Chronic pain	-0.187	0.11	-1.7	0.08909
FMI:Chronic pain	-0.117	0.052	-2.246	0.02472

Supplementary Table B-17. Cross-sectional relationship between fibromyalgia index (FMI) score and Digit-Symbol Substitution Test score, with interaction with chronic pain.

Linear regression beta coefficients (Estimates), 95% confidence intervals (95% CI), and p-values are shown for two models predicting Digit-Symbol Substitution Test performance (centile rank, where higher values indicate better performance) with an interaction with chronic pain. The exposure of interest is the fibromyalgia index (FMI), which is mean centred and a on a scale of 0 to 31. Model 1 adjusts for age, sex, and assessment order. Model 2 includes additional adjustments for sociodemographic factors (education level, Townsend deprivation index, ethnicity, body mass index, and smoking status). Interaction terms (e.g., FMI:Chronic Pain) assess the moderating effect of chronic pain on the relationship between nociplastic pain severity and Digit-Symbol Substitution Test. All continuous variables are mean-centred. `fup_cog0_eop` is the time in years between baseline cognitive assessment at the imaging visit, and response to the online pain questionnaire. Due to non-linearity, this was fitted with a polynomial term.

B.7.1.1.1 Effect modification by sex

In participants with chronic pain, higher FMI scores were associated with lower performance across all three cognitive tasks, with more pronounced associations observed in males than females for the TMT and Matrix tasks (Supplementary Figure B-10). With additional adjustments for ethnicity, socioeconomic status, education, BMI, and tobacco use, the associations remained significant but were slightly attenuated across all tasks. These findings suggest that higher FMI scores are associated with worse cognitive performance in individuals with chronic pain, with stronger effects observed in males across cognitive tasks.

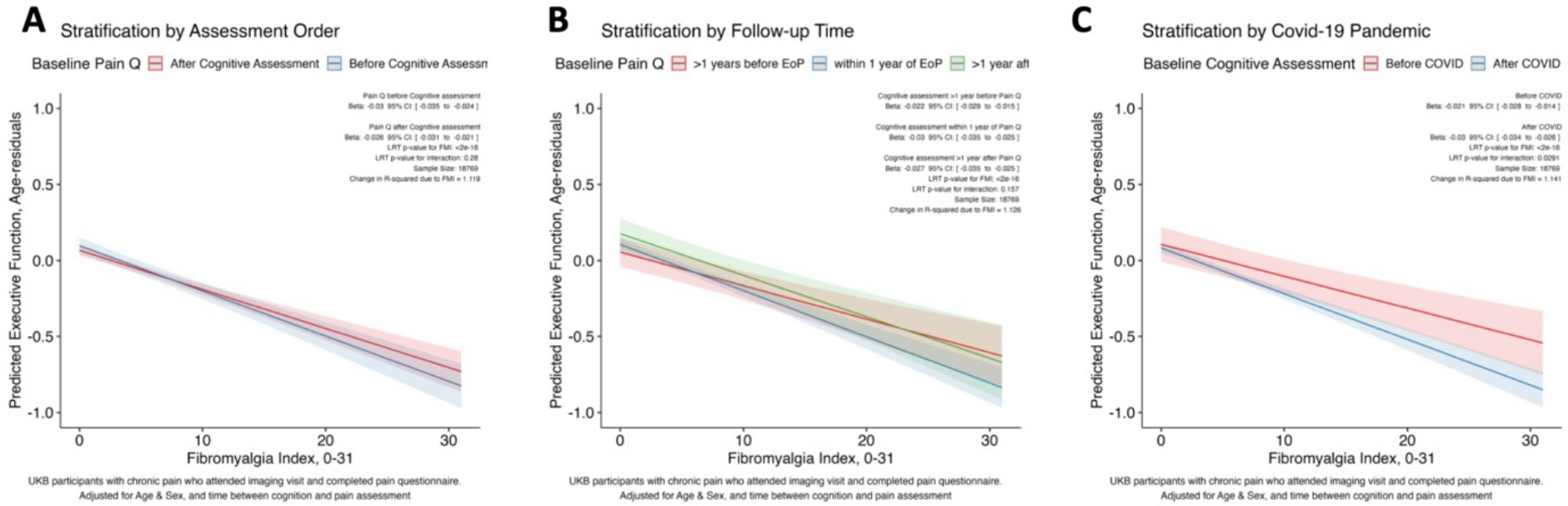


Supplementary Figure B-10. Cross-sectional association between fibromyalgia index (FMI) and cognitive test performance by sex among participants with chronic pain.

Panels show the predicted centile performance on the Trail Making Test (TMT, Panels A and D), Symbol-Digit Substitution (SDS, Panels B and E), and Matrix Pattern Test (Panels C and F) based on FMI scores, stratified by sex. Models in Panels A, B, and C are adjusted for age, sex, and assessment order, while models in Panels D, E, and F include further adjustments for ethnicity, socioeconomic status (SES), education, body mass index (BMI), and tobacco use. Shaded regions represent 95% confidence intervals. The negative association between FMI and cognitive performance is stronger in males across the TMT and Matrix tasks, with significant interactions between FMI and sex as indicated by likelihood ratio test (LRT) p-values for interaction.

B.7.1.2 Assessment time discrepancies & stratification by COVID-19 period

In sensitivity analyses examining the timing of assessments and the impact of the COVID-19 pandemic on the relationship between FMI scores and executive function, consistent results were observed (Supplementary Figure B-11). The negative association between higher FMI scores and worse EF was stable across stratifications by the order of assessments (LRT P-interaction=0.28), the timing relative to the pain questionnaire (LRT P-interaction=0.157), and the pre- versus post-COVID-19 period (LRT P-interaction=0.0291). While a slightly stronger association was noted post-COVID, the overall relationship remained robust across all contexts, supporting the stability of the findings.



Supplementary Figure B-11. Timing of cognitive assessments in relation to pain assessment and COVID-19 pandemic does not change interpretation of results.

Sensitivity analyses of the relationship between Fibromyalgia Index (FMI) score and executive function stratified by assessment timing and external factors. Predicted executive function (age-residuals) is plotted against FMI scores for UK Biobank participants with chronic pain. Panel A shows stratification by assessment order, distinguishing whether the pain questionnaire was administered before or after cognitive testing. Panel B presents stratification by the timing of cognitive assessments relative to the pain assessment (Experience of Pain questionnaire, EoP). Panel C illustrates stratification by the timing of assessments relative to the COVID-19 pandemic. Shaded areas represent 95% confidence intervals. All models adjust for age, sex, and the time elapsed between cognition and pain assessments. The results indicate that the association between higher FMI scores and poorer EF is consistent across different assessment timings and external contexts, suggesting the robustness of this relationship.

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Variable	Field ID	Instance	Comments
Age at imaging	21003	2	
Sex	31	0	
Ethnicity	21000	2	Binarised to white or non-white. Imputed with instance 0 if missing at 2
Townsend Deprivation Index	22189	0	
Education	6138	2	Binarised to University Degree and No Degree. Instance 0 or 10722 used if 6138 missing.
Employment status	6142	2	Binarised to employed or not employed
Smoking	20116	2	Binarised to current smoking or not current smoker
Alcohol use	1558	2	Binarised to current alcohol use or no current alcohol use
BMI	21001	2	Instance 0 or 23104 used if 21001 missing
Sleep duration	1160	2	
Insomnia symptoms	1200	2	
Neuroticism		2	Sum of 1920-2030 (see Smith et al. (2013))
Mood swings	1920	2	
Miserableness	1930	2	
Irritability	1940	2	
Sensitivity / hurt feelings	1950	2	
Fed-up feelings	1960	2	
Nervous feelings	1970	2	
Worrier / anxious feelings	1980	2	
Tense / 'highly strung'	1990	2	
Worry too long after embarrassment	2000	2	
Suffer from 'nerves'	2010	2	
Loneliness, isolation	2020	2	
Guilty feelings	2030	2	
Chronic pain at imaging		2	Answered "Yes" to any of 3799, 3403, 3571, 3741, 3414, 3773 or 2956.
Headaches for 3+ months	3799	2	
Facial pain for 3+ months	4067	2	
Neck/shoulder pain for 3+ months	3403	2	
Back pain for 3+ months	3571	2	
Stomach/Abdominal pain for 3+ months	3741	2	

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Variable	Field ID	Instance	Comments
Hip pain for 3+ months	3414	2	
Knee pain for 3+ months	3773	2	
General pain for 3+ months	2956	2	
Number of pain sites at imaging		2	Sum of 3799, 3403, 3571, 3741, 3414 and 3773.
Fibromyalgia Index		PQ	Sum of Widespread Pain Index and Symptom Severity Scale
Widespread Pain Index	120039	PQ	
Fatigue (SSS)	120040	PQ	
Unrefreshing sleep (SSS)	120041	PQ	
Cognitive difficulties (SSS)	120042	PQ	
Abdominal pain (SSS)	120043	PQ	
Depression (SSS)	120044	PQ	
Headache (SSS)	120045	PQ	
Symptom severity Scale		PQ	sum of 120039-120045
Depression (PHQ-9)	120104 - 120112	PQ	Sum of 120104-120112
Fatigue Severity Scale (FSS)	120119 - 120127	PQ	Sum of 120119-120127, not answered if 120018 is "No" and 120040 is "No problem". In that case the variable was set at the minimum value (i.e. 9)
Executive function			
Trail making test at baseline		2	Difference between trail A & B
Time taken for trail A	6348	2	
Time taken for trail B	6350	2	
Digit symbol substitution test at baseline			Proportion of attempts correct
Number of attempts	23323	2	
Number correct	23324	2	
Matrix Pattern test at baseline			Proportion of attempts correct
Number of attempts	6374	2	
Number correct	7373	2	

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Variable	Field ID	Instance	Comments
Date of Pain Questionnaire	120128	PQ	
Age at pain assessment			Derived from field 31 and date of PQ
Follow-up time from imaging to pain questionnaire			The difference between baseline date (53) and pain questionnaire date (120128)
Exclusion	20002	2	If contained codes: 1262 (dementia), 1263 (Parkinson's), 1289 (psychosis), or 1291 (bipolar disorder)
Imaging confounds			
scan_date	53	2	scan date
Site	54	2	imaging site
Age	21003	2	age
Sex	31	2	sex
HeadSize	25000	2	head size scaling
TablePos_Table	25759	2	scanner table position
TablePos_COG_X	25756	2	Head centre of gravity in scanner coordinates (X)
TablePos_COG_Y	25757	2	Head centre of gravity in scanner coordinates (Y)
TablePos_COG_Z	25758	2	Head centre of gravity in scanner coordinates (Z)
HeadMotion_mean_rfMRI_rel	25741	2	head motion in resting fMRI (mean relative motion as calculated by FEAT)

Supplementary Table C-1. Field IDs for variables from UK Biobank used in the analysis in Chapter 4.

Instance 2, imaging visit. PQ, 2019 pain questionnaire.

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	Total	No Chronic pain	Chronic pain
	(N=33027)	(N=15305)	(N=17722)
Female, N (%)	17829 (54 %)	7645 (50 %)	10184 (57 %)
Age, mean (SD) years	64.2 (7.64)	64.1 (7.66)	64.3 (7.62)
Townsend Deprivation Index, mean (SD)	-1.90 (2.71)	-1.97 (2.67)	-1.85 (2.75)
Married/Partner N (%)	24650 (75 %)	11510 (75 %)	13140 (74 %)
Employment status			
Employed	12365 (37 %)	5911 (39 %)	6454 (36 %)
Retired	19245 (58 %)	8828 (58 %)	10417 (59 %)
Unemployed/Other	1223 (4 %)	488 (3 %)	735 (4 %)
White Ethnicity, N (%)	32201 (97.5%)	14938 (97.6%)	17261 (97.4%)
University Degree, N (%)	16777 (50.8%)	8174 (53.4%)	8613 (48.6%)
Current tobacco use, N (%)	1044 (3.2%)	462 (3.0%)	581 (3.3%)
Alcohol Use			
Never	2103 (6 %)	916 (6 %)	1187 (7 %)
Rarely	7206 (22 %)	3081 (20 %)	4125 (23 %)
Weekly	17966 (54 %)	8576 (56 %)	9390 (53 %)
Daily	5552 (17 %)	2651 (17 %)	2901 (16 %)
Body Mass Index, mean (SD) kg/m2	26.4 (4.37)	25.9 (4.06)	26.8 (4.57)
Fibromyalgia Index (0-31), mean (SD)	3.69 (3.59)	1.97 (1.94)	5.18 (4.00)
Widespread Pain Index (0-19), mean (SD)	1.32 (2.03)	0.278 (0.753)	2.22 (2.33)
Symptom Severity Scale (0-12), mean (SD)	2.37 (2.13)	1.69 (1.65)	2.96 (2.31)

Supplementary Table C-2. Baseline characteristics of participants included in analysis of structural DPMS connectivity and nociplastic pain severity.

Sociodemographic, lifestyle, pain-related, and cognitive performance metrics are summarised for participants in the structural connectivity (N=33,027) group. Results are presented as percentages, means with standard deviations (SD), or medians with ranges, as appropriate. Higher values of Townsend Deprivation Index indicate greater social deprivation. Nociplastic pain assessed using the fibromyalgia index (FMI), with higher scores indicating more severe nociplastic pain. The FMI is the sum of the widespread pain index (WPI) and symptom severity scale (SSS). SD, standard deviation.

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		Structural Connectivity Analysis		
	Total	**Excluded**	**Included**	**P-value**
	(N=41411)	(N=8384)	(N=33027)	
Sex				
Female	22375 (54 %)	4546 (54 %)	17829 (54 %)	0.935
Male	19036 (46 %)	3838 (46 %)	15198 (46 %)	
Age (years)				
Mean (SD)	64.7 (7.61)	66.5 (7.19)	64.2 (7.64)	<0.001
Townsend Deprivation Index				
Mean (SD)	-1.90 (2.73)	-1.90 (2.78)	-1.90 (2.71)	0.979
Marital status				
Married/Partner	30866 (75 %)	6216 (74 %)	24650 (75 %)	0.588
Not married	10228 (25 %)	2108 (25 %)	8120 (25 %)	
Employment status				
Employed	15087 (36 %)	2722 (32 %)	12365 (37 %)	<0.001
Retired	24580 (59 %)	5335 (64 %)	19245 (58 %)	
Unemployed/Other	1509 (4 %)	286 (3 %)	1223 (4 %)	
Ethnicity				
Mean (SD)	0.974 (0.159)	0.970 (0.169)	0.975 (0.156)	0.0582
University Degree				
Mean (SD)	0.515 (0.500)	0.543 (0.498)	0.508 (0.500)	<0.001
Current tobacco use, %				
Mean (SD)	0.0305 (0.172)	0.0265 (0.161)	0.0316 (0.175)	0.053
Alcohol Use				
Never	2695 (7 %)	592 (7 %)	2103 (6 %)	0.476
Rarely	9010 (22 %)	1804 (22 %)	7206 (22 %)	
Weekly	22493 (54 %)	4527 (54 %)	17966 (54 %)	
Daily	6971 (17 %)	1419 (17 %)	5552 (17 %)	
Body Mass Index (kg/m2)				
Mean (SD)	26.3 (4.38)	26.2 (4.43)	26.4 (4.37)	0.00525
Fibromyalgia Index (0-31)				
Mean (SD)	3.66 (3.55)	3.53 (3.37)	3.69 (3.59)	<0.001
Widespread Pain Index (0-19)				
Mean (SD)	1.30 (2.00)	1.21 (1.89)	1.32 (2.03)	<0.001
Symptom Severity Scale (0-12)				
Mean (SD)	2.36 (2.11)	2.31 (2.05)	2.37 (2.13)	0.0987

Supplementary Table C-3. Baseline characteristics for those included in structural connectivity analysis compared to those excluded due to unavailable data.

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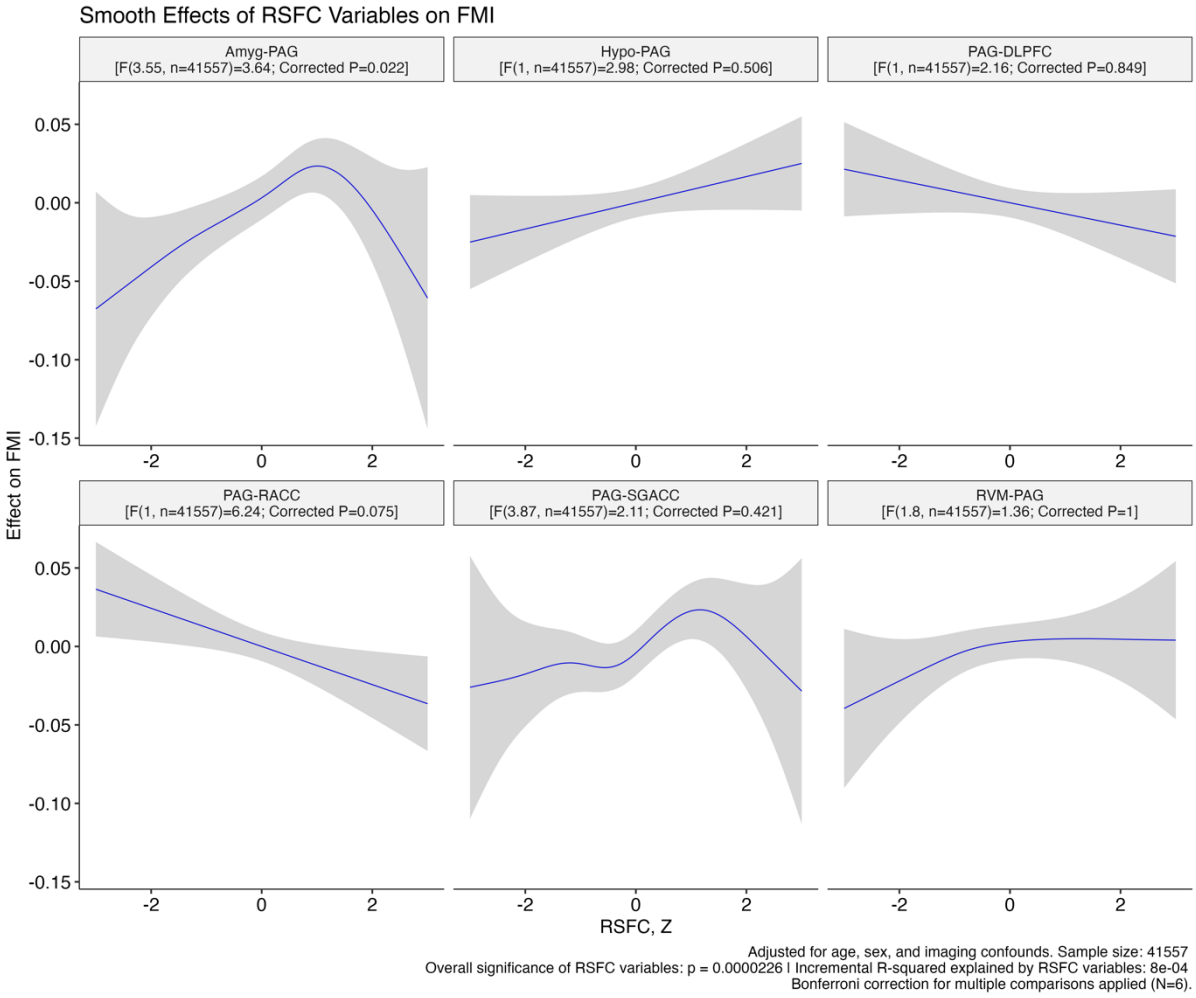

Supplementary Figure C-1. Functional connectivity in the DPMS is associated with nociplastic pain severity (minimally-adjusted model).

Smooth effects of resting-state functional connectivity (RSFC) variables on nociplastic pain severity (fibromyalgia index, FMI). Each panel represents a separate RSFC variable. The blue line indicates the smoothed relationship between RSFC and FMI, with the shaded area representing the 95% confidence interval. All scales are standardised to mean=0, SD=1. Significant effects are shown for the PAG-amygdala RSFC, with other RSFC variables showing non-significant relationships after correction for multiple comparisons. Adjusted for age, sex, and imaging confounds (head size, table position, scan date, scan site, and head motion). PAG, periaqueductal grey. RVM, rostral ventromedial medulla. Amyg, amygdala. Hypo, hypothalamus. rACC, rostral anterior cingulate cortex. sgACC, subgenual anterior cingulate cortex. dlPFC, dorsolateral prefrontal cortex.

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	Minimally-adjusted				Fully-adjusted			
Parametric Terms	**Estimate**	**SE**	**T value**	**P**	**Estimate**	**SE**	**T value**	**P**
(Intercept)	-0.134	0.010	-12.730	0.00000	-0.010	0.036	-0.276	0.78268
sexFemale	0.301	0.013	23.742	0.00000	0.287	0.014	19.978	0.00000
site_Reading	-0.106	0.017	-6.282	0.00000	-0.149	0.019	-7.669	0.00000
site_Newcastle	-0.032	0.015	-2.064	0.03901	-0.038	0.017	-2.319	0.02038
site_Bristol	-0.024	0.027	-0.881	0.37829	0.237	0.151	1.564	0.11772
University Degree					-0.114	0.011	-10.410	0.00000
White Ethnicity					-0.048	0.035	-1.361	0.17359
Current Smoker					0.127	0.031	4.111	0.00004
Smooth terms	**Effective DF**	**Reference DF**	**F value**	**P**	**Effective DF**	**Reference DF**	**F value**	**P**
s(rvmpag.z.w)	1.636	2.067	1.169	0.32783	3.974	4.902	0.862	0.53595
s(amygpag.z.w)	3.605	4.548	3.548	0.00422	1.000	1.000	6.623	0.01007
s(hypopag.z.w)	1.000	1.000	2.941	0.08635	1.242	1.445	4.763	0.01430
s(pagracc.z.w)	1.000	1.000	6.456	0.01106	1.000	1.000	4.280	0.03856
s(pagsgacc.z.w)	3.962	4.972	2.020	0.07709	1.000	1.000	11.553	0.00068
s(pagdlpfc.z.w)	1.000	1.000	2.017	0.15560	1.674	2.118	4.862	0.00648
s(age.z)	3.014	3.799	106.465	0.00000	3.063	3.851	45.638	0.00000
s(HeadSize.z)	2.973	3.791	9.528	0.00000	1.000	1.000	28.525	0.00000
s(TablePos_COG_X.z)	1.000	1.000	0.000	0.99405	1.000	1.000	1.358	0.24394
s(TablePos_COG_Y.z)	3.479	4.370	5.631	0.00012	1.000	1.000	3.526	0.06041
s(TablePos_COG_Z.z)	2.315	2.970	4.271	0.00601	1.685	2.138	1.271	0.26407
s(ScanDay.z)	8.549	8.940	2.399	0.02040	1.499	1.846	3.107	0.02941
s(HeadMotion_mean_rfMRI_rel.z)	5.736	6.933	92.356	0.00000	6.065	7.268	2.806	0.00490
s(tdi)					4.945	6.011	24.266	0.00000

s(bmi.z)					3.315	4.238	120.118	0.00000

Supplementary Table C-4. Summary of parametric and smooth terms in minimally- and fully-adjusted GAM models for functional connectivity.

Results from two Generalised Additive Models (GAM): a minimally adjusted model and a fully adjusted model. Outcome is nociplastic pain severity, FMI. The parametric terms include predictors such as sex and site of data collection, with their corresponding regression estimates, standard errors (SE), t-values, and p-values. These terms represent the linear relationships between the predictors and the outcome variable. Smooth terms describe non-linear relationships and are characterised by effective degrees of freedom (EDF), reference degrees of freedom (Ref.df), F-values, and p-values. The effective degrees of freedom (EDF) indicate the complexity of the smooth terms, where a value close to 1 suggests a linear relationship, and higher values reflect greater non-linearity. The predictors include functional connectivity measures (rvmpag.z.w, amygpag.z.w, etc.), brain structural attributes (e.g., HeadSize.z, TablePos_COG_X.z), and demographic variables (e.g., sex, site, and smoking status). All continuous variables centred and standardised. EDF (Effective Degrees of Freedom), Ref.df (Reference Degrees of Freedom), COG (Centre of Gravity), and functional connectivity measures (e.g., rvmpag.z.w) corresponding to specific brain regions.

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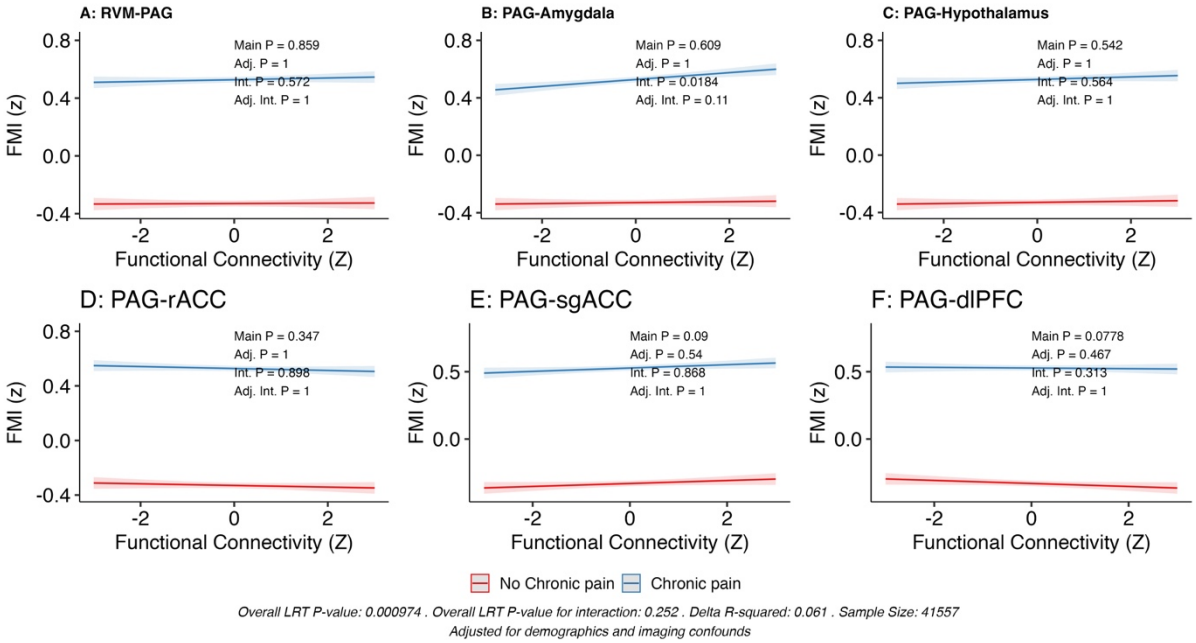

Supplementary Figure C-2. No interaction between chronic pain status and DPMS functional connectivity on nociplastic pain severity (minimally-adjusted model)

Interaction effects of resting-state functional connectivity (RSFC) variables with chronic pain status on nociplastic pain severity (Fibromyalgia Index, FMI) in the fully adjusted model. Each panel represents a separate RSFC variable, with the blue (chronic pain) and red (no chronic pain) lines showing the predicted relationship between RSFC and FMI. All scales are standardised to mean=0, SD=1. Shaded areas indicate the 95% confidence intervals. Adjusted for age, sex, imaging confounds (head size, table position, scan date, scan site, and head motion). PAG, periaqueductal grey. RVM, rostral ventromedial medulla. Amyg, amygdala. Hypo, hypothalamus. rACC, rostral anterior cingulate cortex. sgACC, subgenual anterior cingulate cortex. dlPFC, dorsolateral prefrontal cortex.

Appendix C

	Minimally-adjusted				Fully-adjusted			
Term	**Estimate**	**SE**	**T value**	**P**	**Estimate**	**SE**	**T value**	**P**
(Intercept)	-0.562	0.010	-56.011	0.00000	-0.456	0.029	-15.903	0.00000
rvmpag.z.w	0.001	0.006	0.185	0.85348	0.002	0.006	0.350	0.72653
amygpag.z.w	0.003	0.006	0.474	0.63581	0.004	0.006	0.630	0.52901
hypopag.z.w	0.004	0.006	0.605	0.54538	0.004	0.006	0.609	0.54282
pagracc.z.w	-0.006	0.006	-0.898	0.36943	-0.004	0.006	-0.629	0.52931
pagsgacc.z.w	0.011	0.006	1.697	0.08968	0.011	0.006	1.769	0.07697
pagdlpfc.z.w	-0.011	0.006	-1.747	0.08058	-0.011	0.006	-1.696	0.08995
cp_eop_binChronic pain	0.857	0.009	98.394	0.00000	0.837	0.009	96.442	0.00000
age.z	-0.098	0.005	-21.433	0.00000	-0.078	0.005	-16.709	0.00000
sexFemale	0.232	0.011	20.763	0.00000	0.237	0.011	21.298	0.00000
site_Reading	-0.070	0.014	-5.016	0.00000	-0.070	0.014	-4.939	0.00000
site_Newcastle	-0.033	0.013	-2.580	0.00988	-0.016	0.013	-1.277	0.20155
site_Bristol	-0.009	0.024	-0.359	0.71933	0.009	0.024	0.371	0.71076
HeadSize.z	0.023	0.006	4.128	0.00004	0.022	0.006	3.982	0.00007
TablePos_COG_X.z	0.000	0.004	-0.072	0.94222	-0.002	0.004	-0.400	0.68909
TablePos_COG_Y.z	0.021	0.006	3.738	0.00019	0.010	0.006	1.739	0.08211
TablePos_COG_Z.z	-0.011	0.005	-2.381	0.01729	-0.006	0.005	-1.222	0.22164
ScanDay.z	0.003	0.006	0.527	0.59837	0.008	0.006	1.426	0.15401
HeadMotion_mean_rfMRI_rel.z	0.096	0.004	21.508	0.00000	0.027	0.005	4.946	0.00000
degree_bin					-0.090	0.009	-10.297	0.00000
baseline_white					-0.061	0.028	-2.204	0.02750
tdi.z					0.058	0.004	13.168	0.00000
baseline_smoker					0.095	0.025	3.801	0.00014

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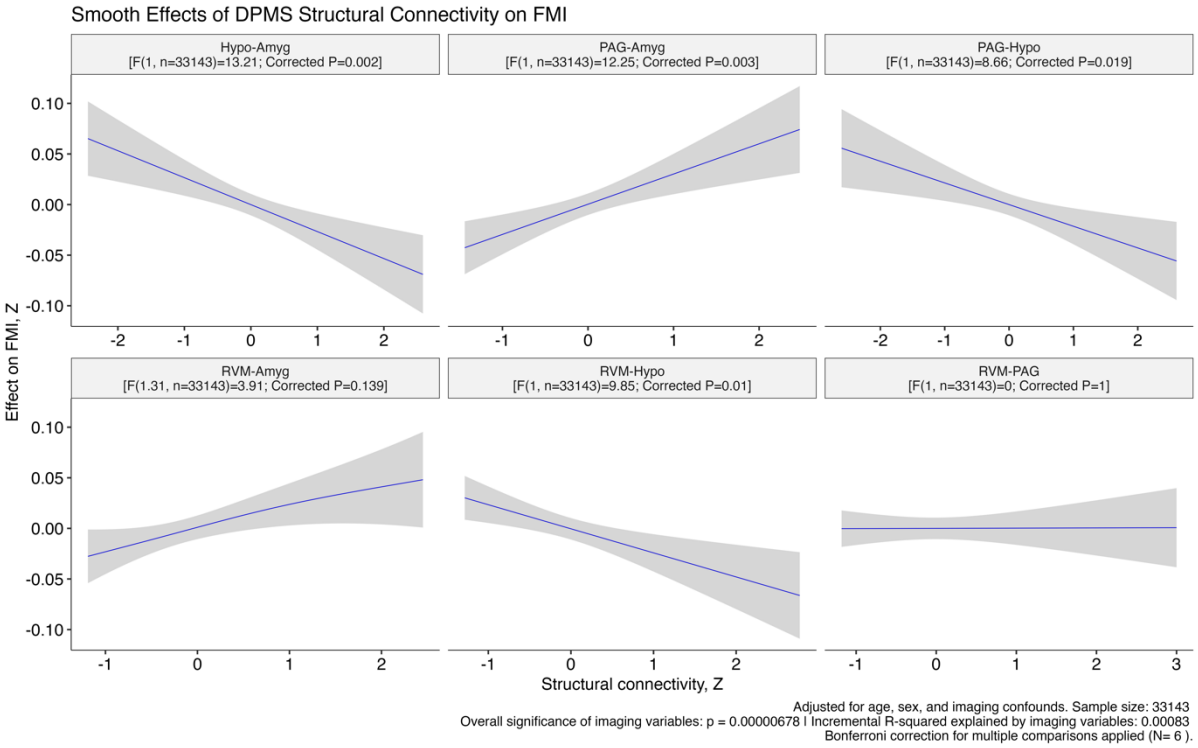
	Minimally-adjusted				Fully-adjusted			
Term	**Estimate**	**SE**	**T value**	**P**	**Estimate**	**SE**	**T value**	**P**
bmi.z					0.099	0.005	18.164	0.00000
rvmpag.z.w:cp_eop_binChronic pain	0.005	0.009	0.523	0.60072	0.005	0.009	0.585	0.55850
amygpag.z.w:cp_eop_binChronic pain	0.020	0.009	2.318	0.02047	0.019	0.009	2.217	0.02665
hypopag.z.w:cp_eop_binChronic pain	0.005	0.009	0.555	0.57891	0.005	0.009	0.598	0.54964
pagracc.z.w:cp_eop_binChronic pain	-0.002	0.009	-0.201	0.84057	-0.002	0.009	-0.249	0.80345
pagsgacc.z.w:cp_eop_binChronic pain	0.001	0.009	0.127	0.89878	0.000	0.009	0.028	0.97743
pagdlpfc.z.w:cp_eop_binChronic pain	0.009	0.009	1.029	0.30370	0.010	0.009	1.145	0.25218

Supplementary Table C-5. Summary of linear regression analysis with interaction with DPMS functional connectivity and chronic pain status.

Results from two linear regression models: a minimally adjusted model and a fully adjusted model. Outcome is nociplastic pain severity, FMI. The parametric terms include predictors such as sex and site of data collection, with their corresponding regression estimates, standard errors (SE), t-values, and p-values. The predictors include functional connectivity measures (rvmpag.z.w, amygpag.z.w, etc.), brain structural attributes (e.g., HeadSize.z, TablePos_COG_X.z), and demographic variables (e.g., sex, site, and smoking status). All continuous variables centred and standardised. COG (Centre of Gravity), and functional connectivity measures (e.g., rvmpag.z.w) corresponding to specific brain regions.



Supplementary Figure C-3. Structural connectivity in DPMS predicts nociplastic pain severity (minimally-adjusted model)

Smooth effects of structural connectivity variables in the descending pain modulatory system (DPMS) on nociplastic pain severity (Fibromyalgia Index, FMI) in the minimally adjusted model. Each panel represents a distinct structural connectivity pair, with the blue line indicating the smoothed relationship between connectivity and FMI, and the shaded region representing the 95% confidence interval. All scales are standardised to mean=0, SD=1. Significant associations are highlighted in the text. Adjusted for age, sex, and imaging confounds (head size, table position, scan date, scan site, and head motion). PAG, periaqueductal grey; RVM, rostral ventromedial medulla; Amyg, amygdala; Hypo, hypothalamus.

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	Minimally-adjusted				Fully-adjusted			
Parametric Terms	**Estimate**	**SE**	**T value**	**P**	**Estimate**	**SE**	**T value**	**P**
(Intercept)	-0.118	0.012	-10.140	0.00000	-0.010	0.036	-0.276	0.78268
sexFemale	0.302	0.014	20.963	0.00000	0.287	0.014	19.978	0.00000
site_Reading	-0.139	0.020	-6.975	0.00000	-0.149	0.019	-7.669	0.00000
site_Newcastle	-0.048	0.017	-2.753	0.00590	-0.038	0.017	-2.319	0.02038
site_Bristol	0.232	0.153	1.516	0.12965	0.237	0.151	1.564	0.11772
University Degree					-0.114	0.011	-10.410	0.00000
White Ethnicity					-0.048	0.035	-1.361	0.17359
Current Smoker					0.127	0.031	4.111	0.00004
Smooth terms	**Effective DF**	**Reference DF**	**F value**	**P**	**Effective DF**	**Reference DF**	**F value**	**P**
s(RVM.PAG.z.w)	3.621	4.482	0.603	0.63727	3.974	4.902	0.862	0.53595
s(RVM.Hypo.z.w)	1.000	1.000	9.522	0.00203	1.000	1.000	6.623	0.01007
s(RVM.Amyg.z.w)	1.110	1.211	5.092	0.01634	1.242	1.445	4.763	0.01430
s(PAG.Hypo.z.w)	1.000	1.000	9.372	0.00221	1.000	1.000	4.280	0.03856
s(PAG.Amyg.z.w)	1.000	1.000	12.895	0.00033	1.000	1.000	11.553	0.00068
s(Hypo.Amyg.z.w)	1.000	1.000	13.687	0.00022	1.674	2.118	4.862	0.00648
s(age.z)	3.065	3.854	91.543	0.00000	3.063	3.851	45.638	0.00000
s(HeadSize.z)	1.000	1.000	26.209	0.00000	1.000	1.000	28.525	0.00000
s(TablePos_COG_X.z)	1.000	1.000	2.072	0.15004	1.000	1.000	1.358	0.24394
s(TablePos_COG_Y.z)	3.204	4.042	4.759	0.00074	1.000	1.000	3.526	0.06041
s(TablePos_COG_Z.z)	2.330	2.990	5.211	0.00150	1.685	2.138	1.271	0.26407
s(ScanDay.z)	1.991	2.484	2.585	0.04423	1.499	1.846	3.107	0.02941
s(HeadMotion_mean_rfMRI_rel.z)	6.283	7.398	68.656	0.00000	6.065	7.268	2.806	0.00490
s(tdi)					4.945	6.011	24.266	0.00000

s(bmi.z)					3.315	4.238	120.118	0.00000

Supplementary Table C-6. Summary of parametric and smooth terms in minimally- and fully-adjusted GAM models for structural connectivity.

Results from two Generalised Additive Models (GAM): a minimally adjusted model and a fully adjusted model. Outcome is nociplastic pain severity, FMI. The parametric terms include predictors such as sex and site of data collection, with their corresponding regression estimates, standard errors (SE), t-values, and p-values. These terms represent the linear relationships between the predictors and the outcome variable. Smooth terms describe non-linear relationships and are characterised by effective degrees of freedom (EDF), reference degrees of freedom (Ref.df), F-values, and p-values. The effective degrees of freedom (EDF) indicate the complexity of the smooth terms, where a value close to 1 suggests a linear relationship, and higher values reflect greater non-linearity. The predictors include functional connectivity measures (RVM.PAG.z.w, RVM.Hypo.z.w, etc.), brain structural attributes (e.g., HeadSize.z, TablePos_COG_X.z), and demographic variables (e.g., sex, site, and smoking status). All continuous variables centred and standardised. EDF (Effective Degrees of Freedom), Ref.df (Reference Degrees of Freedom), COG (Centre of Gravity), and structural connectivity measures (e.g., RVM.PAG.z.w) corresponding to specific brain regions.

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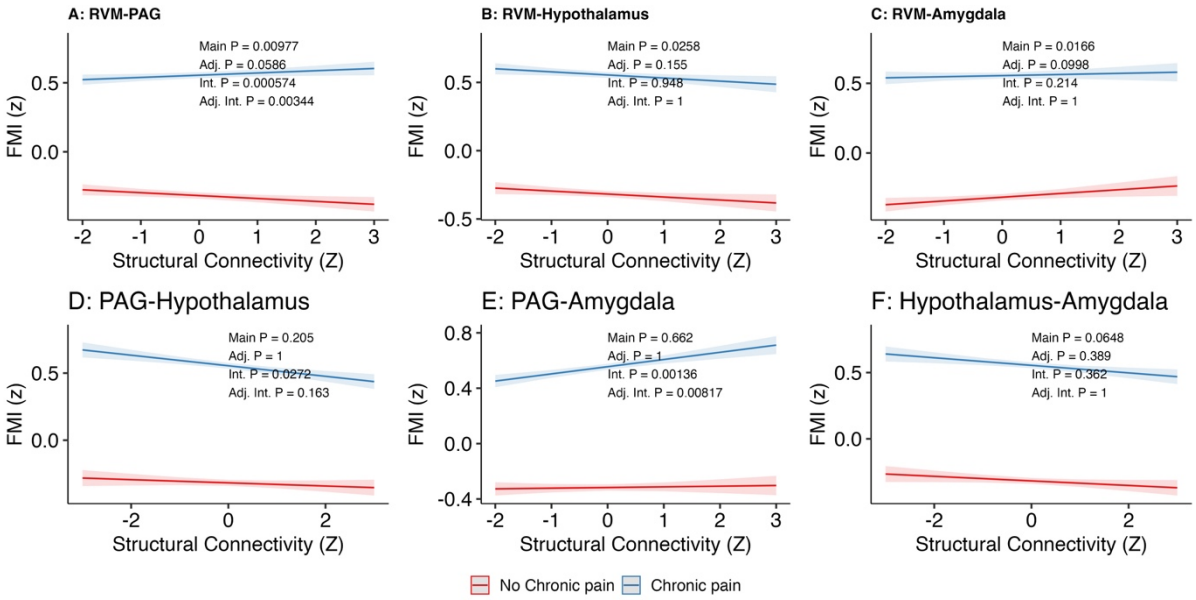

Supplementary Figure C-4. Chronic pain moderates the association between structural connectivity and nociplastic pain severity (minimally-adjusted model).

Interaction effects of structural connectivity (SC) variables with chronic pain status on nociplastic pain severity (Fibromyalgia Index, FMI) in the minimally adjusted model. Each panel represents a separate SC variable, with the blue (chronic pain) and red (no chronic pain) lines showing the predicted relationship between SC and FMI. All scales are standardised to mean=0, SD=1. Shaded areas indicate the 95% confidence intervals. Adjusted for age, sex, and imaging confounds (head size, table position, scan date, scan site, and head motion). PAG, periaqueductal grey; RVM, rostral ventromedial medulla; Amyg, amygdala; Hypo, hypothalamus.

Appendix C

	Minimally-adjusted				Fully-adjusted			
Term	**Estimate**	**SE**	**T value**	**P**	**Estimate**	**SE**	**T value**	**P**
(Intercept)	-0.458	0.033	-13.750	0.00000	-0.548	0.013	-43.520	0.00000
RVM.PAG.z.w	-0.020	0.008	-2.437	0.01480	-0.021	0.008	-2.583	0.00980
RVM.Hypo.z.w	-0.018	0.010	-1.887	0.05912	-0.021	0.010	-2.167	0.03024
RVM.Amyg.z.w	0.026	0.011	2.300	0.02143	0.027	0.011	2.369	0.01783
PAG.Hypo.z.w	-0.008	0.009	-0.858	0.39085	-0.012	0.009	-1.276	0.20205
PAG.Amyg.z.w	0.004	0.011	0.341	0.73315	0.005	0.011	0.425	0.67108
Hypo.Amyg.z.w	-0.012	0.009	-1.310	0.19034	-0.018	0.009	-1.875	0.06078
cp_eop_binChronic pain	0.852	0.010	86.647	0.00000	0.873	0.010	88.498	0.00000
age.z	-0.084	0.005	-15.380	0.00000	-0.106	0.005	-19.762	0.00000
sexFemale	0.239	0.013	18.555	0.00000	0.237	0.013	18.322	0.00000
site_Reading	-0.114	0.017	-6.525	0.00000	-0.115	0.017	-6.651	0.00000
site_Newcastle	-0.034	0.015	-2.316	0.02056	-0.051	0.015	-3.426	0.00061
site_Bristol	0.227	0.137	1.662	0.09647	0.226	0.138	1.639	0.10130
HeadSize.z	0.023	0.006	3.600	0.00032	0.025	0.006	3.875	0.00011
TablePos_COG_X.z	0.006	0.005	1.090	0.27579	0.007	0.005	1.370	0.17060
TablePos_COG_Y.z	0.006	0.007	0.970	0.33192	0.018	0.007	2.707	0.00679
TablePos_COG_Z.z	-0.004	0.005	-0.792	0.42830	-0.010	0.005	-1.843	0.06535
ScanDay.z	0.033	0.010	3.498	0.00047	0.026	0.010	2.665	0.00770
HeadMotion_mean_rfMRI_rel.z	0.026	0.006	4.063	0.00005	0.096	0.005	18.859	0.00000
degree_bin	-0.092	0.010	-9.263	0.00000				
baseline_white	-0.040	0.032	-1.254	0.21002				
tdi.z	0.059	0.005	11.749	0.00000				
baseline_smoker	0.109	0.028	3.885	0.00010				

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	Minimally-adjusted				Fully-adjusted			
Term	**Estimate**	**SE**	**T value**	**P**	**Estimate**	**SE**	**T value**	**P**
bmi.z	0.104	0.006	16.563	0.00000				
RVM.PAG.z.w:cp_eop_binChronic pain	0.036	0.011	3.315	0.00092	0.037	0.011	3.438	0.00059
RVM.Hypo.z.w:cp_eop_binChronic pain	0.001	0.013	0.084	0.93274	-0.001	0.013	-0.084	0.93322
RVM.Amyg.z.w:cp_eop_binChronic pain	-0.016	0.015	-1.031	0.30265	-0.019	0.015	-1.236	0.21663
PAG.Hypo.z.w:cp_eop_binChronic pain	-0.025	0.012	-1.983	0.04739	-0.028	0.012	-2.233	0.02555
PAG.Amyg.z.w:cp_eop_binChronic pain	0.046	0.015	3.163	0.00157	0.048	0.015	3.255	0.00114
Hypo.Amyg.z.w:cp_eop_binChronic pain	-0.012	0.012	-0.990	0.32222	-0.011	0.012	-0.908	0.36371

Supplementary Table C-7. Summary of linear regression analysis with interaction with DPMS structural connectivity and chronic pain status.

Results from two linear regression models: a minimally adjusted model and a fully adjusted model. Outcome is nociplastic pain severity, FMI. The parametric terms include predictors such as sex and site of data collection, with their corresponding regression estimates, standard errors (SE), t-values, and p-values. The predictors include functional connectivity measures (RVM.PAG.z.w, RVM.Hypo.z.w, etc.), brain structural attributes (e.g., HeadSize.z, TablePos_COG_X.z), and demographic variables (e.g., sex, site, and smoking status). All continuous variables centred and standardised. COG (Centre of Gravity), and structural connectivity measures (e.g., RVM.PAG.z.w) corresponding to specific brain regions

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Path	Estimate	SE	CI Lower	CI Upper	z-value	Uncorrected P	Corrected P
indirect_rvmpag	0.0000	0.0011	-0.0021	0.0021	0.0350	0.97211	1.00000
indirect_amygpag	-0.0023	0.0008	-0.0038	-0.0008	-2.9667	0.00301	0.01806
indirect_hypopag	-0.0008	0.0007	-0.0022	0.0006	-1.0935	0.27417	1.00000
indirect_pagracc	0.0006	0.0005	-0.0003	0.0015	1.2805	0.20038	1.00000
indirect_pagsgacc	-0.0011	0.0006	-0.0023	0.0000	-1.9387	0.05253	0.31520
indirect_pagdlpfc	0.0004	0.0006	-0.0008	0.0017	0.7128	0.47594	1.00000
direct	-0.1089	0.0161	-0.1405	-0.0773	-6.7567	0.00000	

Supplementary Table C-8. Mediation of FMI on EF via DPMS functional connectivity

This table presents the results of the mediation analysis of nociplastic pain severity (FMI) on executive function (EF) via DPMS functional connectivity pathways, detailing both direct and indirect effects of DPMS connectivity pathways on EF. Indirect paths, such as indirect_rvmpag and indirect_amygpag, represent mediating effects through specific DPMS pairs, while the direct path captures the unmediated relationship between FMI and EF. Each path is characterised by its standardised parameter estimate, standard error (SE), 95% confidence intervals (CI Lower, CI Upper), z-value, and p-values. The uncorrected p-values are provided alongside Bonferroni corrected p-values, which account for multiple comparisons using.

Path	Estimate	SE	CI Lower	CI Upper	z-value	Uncorrected P	Corrected P
indirect_rvmpag	-0.0013	0.0011	-0.0035	0.0009	-1.1637	0.2446	1.0000
indirect_rvmhypo	0.0022	0.0011	0.0000	0.0044	1.9229	0.0545	0.3269
indirect_rvmamyg	-0.0003	0.0013	-0.0028	0.0023	-0.2036	0.8387	1.0000
indirect_paghypo	0.0036	0.0008	0.0021	0.0052	4.5481	0.00001	0.00003
indirect_pagamyg	-0.0039	0.0012	-0.0062	-0.0015	-3.2116	0.0013	0.0079
indirect_hypoamyg	0.0010	0.0020	-0.0010	0.0030	0.9550	0.0750	0.4500
direct	-0.1157	0.0121	-0.1395	-0.0919	-9.5251	0.0000	

Supplementary Table C-9. Mediation of FMI on EF via DPMS structural connectivity

This table presents the results of the mediation analysis of nociplastic pain severity (FMI) on executive function (EF) via DPMS structural connectivity pathways, detailing both direct and indirect effects of DPMS connectivity pathways on EF. Indirect paths, such as indirect_rvmpag and indirect_amygpag, represent mediating effects through specific DPMS pairs, while the direct path captures the unmediated relationship between FMI and EF. Each path is characterised by its standardised parameter estimate, standard error (SE), 95% confidence intervals (CI Lower, CI Upper), z-value, and p-values. The uncorrected p-values are provided alongside Bonferroni corrected p-values, which account for multiple comparisons using.

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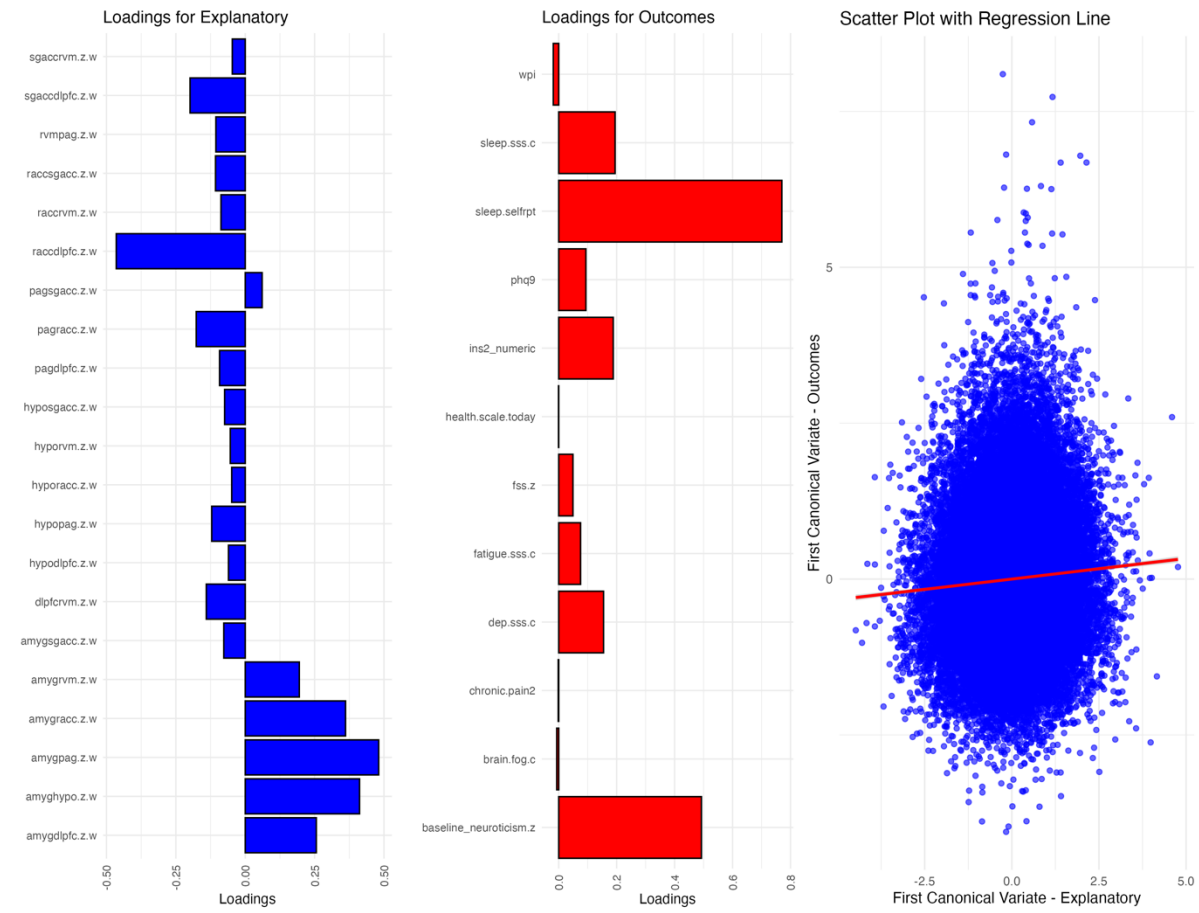

Supplementary Figure C-5. Canonical correlation analysis (CCA) between DPMS connectivity and biopsychosocial variables.

This figure illustrates the results of a canonical correlation analysis (CCA) examining the relationship between descending pain modulatory system (DPMS) connectivity and biopsychosocial characteristics in UK Biobank participants (N=40,405). The left panel displays the loadings for explanatory variables, which represent resting-state functional connectivity (RSFC) between DPMS regions. Positive associations are shown as blue bars pointing to the right, while negative associations are shown as blue bars pointing to the left. The middle panel presents the loadings for outcome variables, which represent biopsychosocial measures. Positive associations are represented by red bars pointing to the right, while negative associations are shown as red bars pointing to the left. The right panel depicts a scatter plot of the first canonical variates for the explanatory (connectivity) and outcome (biopsychosocial) variables, with a regression line to indicate the strength and direction of their relationship.

Acronyms: DPMS (Descending Pain Modulatory System), RSFC (Resting-State Functional Connectivity), PAG (Periaqueductal Grey), rACC (Rostral Anterior Cingulate Cortex), Hypo (Hypothalamus), Amyg (Amygdala), sgACC (Subgenual Anterior Cingulate Cortex), and dlPFC (Dorsolateral Prefrontal Cortex). Biopsychosocial variables include WPI (Widespread Pain Index), SSS (Symptom Severity Score), Sleep.selfrpt (Self-reported sleep duration), PHQ-9 (Patient Health Questionnaire 9-item for depression severity), Ins2_numeric (Insomnia symptom severity score), Health.scale.today (Self-rated health from the EQ-5D-5L visual analogue scale), and Chronic.pain2 (Number of chronic pain sites reported at imaging). CCA refers to Canonical Correlation Analysis.

D Appendix D: Chapter 5

D.1 PainLESS Study: Recruitment materials

Supplementary Figure D-1. Recruitment poster aimed at patients with fibromyalgia

Study of adults with fibromyalgia

We are looking for adults 18 years and older who suffer with fibromyalgia to take part in an observational study.

Many people with fibromyalgia have problems with sleep and cognition such as concentration and memory ('*Fibro-fog*'). This research seeks to better understand these problems.

We believe treating sleep difficulties with **Sleepio** (a sleep therapy app) may help alleviate some of the symptoms of fibromyalgia.

Characterisation of **Pain** in patients with musculoskeletal disease: a prospective, **L**ongitudinal, observational study with an **E**mbedded feasibility window of opportunity **S**leep **S**tudy **(Pain-LESS)**

REC approval: IRAS ID 252762

Principal Investigator: Dr Anushka Soni

Wellcome Centre for Integrative Neuroimaging, John Radcliffe Hospital, Oxford OX3 9DU

Assessments may include

- Online questionnaires *(at home)*
- Cognitive testing *(at home)*
- Sleep monitoring *(at home)*
- Movement analysis *(at home)*
- Brain MRI

Is your patient eligible?

- Diagnosis of fibromyalgia
- 18 years or over

Location

- If they prefer, most assessments can be done at home in their own time
- Up to 2 in-person appointments at **Oxford Centre for Functional MRI of the Brain (FMRIB)**, John Radcliffe Hospital, Headington, Oxford OX3 9D

If you think you have a patient who is eligible, please contact the study team:
fibromyalgia@ndcn.ox.ac.uk
There is no obligation to participate

Supplementary Figure D-2. Recruitment poster aimed at clinicians

D.2 PainLESS Study: Patient Information Sheet

Dr Anushka Soni
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PARTICIPANT INFORMATION SHEET

Title: Characterisation of Pain in patients with musculoskeletal disease: a prospective, Longitudinal, observational study with an Embedded feasibility window of opportunity Sleep Study (Pain-LESS)

We'd like to invite you to take part in our research study. Before you decide, it is important that you understand why the research is being done and what it would involve for you. Please take time to read this information and discuss it with others if you wish. *If there is anything that is not clear, or if you would like more information, please ask us.*

What is the purpose of the study?

The purpose of this study is to better understand pain experienced by patients with a range of musculoskeletal conditions. In particular we would like to investigate how the body's pain detection system in the brain contributes to pain, and whether this influences how a patient responds to current treatments. We would like to assess a novel set of online tools, based on a scientific understanding of how learning works in the brain, in those with chronic musculoskeletal pain. We would also like to better understand the effect of treating disordered sleep on cognitive function (certain processes in the brain such as thinking, decision making and remembering) and sleep quality in people with fibromyalgia, a musculoskeletal condition and cause of chronic pain. The study will last 12 months.

Why have I been invited?

You have been invited because you have been diagnosed with either inflammatory arthritis or fibromyalgia. We are intending to involve 490 people with inflammatory arthritis and 490 people with fibromyalgia. If you have been diagnosed with fibromyalgia, you are likely to experience disturbed sleep or insomnia. We would also like to ask up to 80 people with fibromyalgia and sleep disturbance to take part in a more detailed study investigating the effectiveness of an online sleep intervention.

Do I have to take part?

No. It is entirely up to you whether or not you take part in this study. You will be free to withdraw at any time without giving any reason, without your medical care or legal rights being affected. Whether you participate or not, the study will not affect routine care.

What will happen to me if I decide to take part?

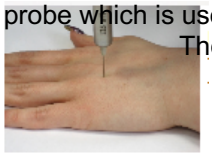
If you are interested in taking part in the study, an investigator will speak to you at your routine clinical visit, or on the phone, to explain the study to you and check whether the study is still relevant to you. If you wish to take part in the study, you will be asked to complete a consent form, on paper in person or remotely if you prefer. In addition to your routine hospital visits, you can choose to take part in additional research visits. The exact number of visits and their duration will depend on your specific condition,

which type of treatment you are starting and which assessments you choose to take part in. The assessments include:
Questionnaires: you will be asked to complete a series of questionnaires which will focus on your pain experiences, and how it affects you. The questionnaires can be completed securely online using any computer and in the comfort of your own home. They should take around 45 minutes to complete.

Quantitative sensory testing: this is a standard research method used to measure people's ability to detect a number of different sensory inputs such as touch, pain and pressure triggers. We will use equipment, shown below, to test different areas of skin. We will not use intensities of sensory inputs that you are unable to tolerate and you will always be able stop the testing at any point, should you wish to. For those with fibromyalgia, heart rate variability (HRV) will also be measured using the validated Camera HRV app on the researcher's mobile phone or iPad. You will be asked to hold your index finger to the phone camera for 5 minutes and the app will record your HRV. This will take 35 to 45 minutes to complete.

Example of a pressure probe which is used to test pressure sensitivity

Punctate probe which is used to test touch sensitivity.
The probe does not penetrate the skin.



Blood sample: Depending on your type of pain, you will be invited to have a blood test. We will take 30mls blood sample (approximately 3 dessert spoons), which will be coded with your ID number only and be stored in a freezer located at Oxford University. Taking blood will take 3 minutes.

Online games: You may be invited to undertake some online games (balloon popping, roadside check, screen touching and ball balancing) which assess different aspects of learning. This can be done on a phone or tablet. Each task will take around 20 minutes.

5 Movement analysis: You may be invited to set up a smart phone or tablet camera at home, or come for a separate visit, to be videoed whilst performing some basic physio-type exercises (whilst holding onto a chair for support: marching on the spot holding, taking your leg out behind you, bending and straightening your knee, squats and heel lifts). You can repeat these as many times as you feel comfortable in 30 seconds. This will take a few minutes. You can still be included in the study if you decline to being recorded.

Cognitive testing: you can choose to complete a series of tests of brain function. These can be completed online using a computer.

Brain scanning: Patients who are able to have a magnetic resonance imaging (MRI) scan done will be invited to take part in this part of the study. Having an MRI scan is optional - you can participate in other parts of the study and not undergo a scan. If you chose to have a scan, a researcher will go through a screening form with you to check if it is safe for you to participate. If you agree, we will ask you to come to the Wellcome Centre for Integrative Neuroimaging at the John Radcliffe Hospital. If you wear glasses or contact lenses, you will be given a pair of MRI-safe glasses to wear. The scanner produces loud banging noises so you will also be given suitable hearing protection (earplugs). In preparation for your scan and for your comfort and safety we will ask you to change into pocketless "pyjama-style" top and trousers, which are available in a range of sizes. You may keep your underwear and socks on, but we would ask ladies to remove underwired bras. If you have a suitable sports type bra you may wear this instead. Metal jewellery, including body piercing, must also be removed. Eye shadow and mascara must also be avoided, since some types contain materials that can interact with the magnetic field. If you wish to wear eye makeup to your scan, we can provide makeup removal wipes, but you are advised to bring your own makeup to reapply. Lockers are provided to secure your personal belongings and clothing. To undergo

scanning you will be asked to lie still on a table inside the MRI scanner. The research would involve having a series of scans, during which you will be asked to respond to specific stimuli. The duration of the scanning period will be 45 minutes.

Online sleep intervention with sleep monitoring: Depending on your type of pain, you can volunteer to be screened for insomnia and to be randomly allocated to either standard treatment of written materials produced by the charity Versus Arthritis, with evidence-based sleep hygiene advice alone, or alongside Sleepio. Sleepio is an online program designed by sleep experts based on cognitive behavioural therapy. The program involves 6 personalised 20-minute sessions over 6 weeks. A period of sleep restriction is often recommended, which can temporarily increase daytime sleepiness. Access to Sleepio will be given to you free of charge, which you can use on a variety of electronic devices including as a mobile phone app or on a computer. We will also be asked you to wear an activity watch and complete a sleep and healthcare usage diary for a series of 7 days before and after Sleepio, to evaluate the quality of your sleep. You may also be invited to take part in a focus group session. These will take place 6 months into the study and will last about 3 hours. You can choose not to participate in this part of the study. These focus group sessions will occur online using Microsoft Teams, and audio recordings will be transcribed using Microsoft Team's software. These recording will then be deleted, and the transcripts will be stored securely on the university servers.

What should I consider?
You may not be able to take part in the study if you have another condition which affects how nerves work, e.g. diabetic neuropathy. You will be able to continue your regular medications as usual but we may ask if it is possible for you stop or delay taking some of your pain related medications around the time of the brain scan as this can affect the results. It will not be a problem if this is not possible for you. You may be able to take part in this study if you are already taking part in another study, but this is something you will need to check with the research team.

Are there any possible disadvantages or risks from taking part?
Taking part in this study will require you to attend the hospital for more visits than you would otherwise need.

In the questionnaires, we will be asking you to give us information about your pain as well as other sensitive topics such as your mood. You are under no obligation to answer these questions if you feel too uncomfortable to do so.

The sensory testing may cause minor, temporary discomfort but you will be in control of the triggers applied and you will be free to stop the assessment at any point in time.

MRI is safe and non-invasive and does not involve any ionising radiation (x-rays). However, because they use a large magnet to work, MRI scans are not suitable for everybody. Because of this, you will be asked pre-screening safety questions to help determine if you are able to take part. For example, if you suffer from claustrophobia, you could not be scanned. Normally, MRI scanning for research purposes would not be performed without further investigation if you have a heart pacemaker, mechanical heart valve, mechanical implant such as an aneurysm clip, hip replacement, or if you carry other pieces of metal that have accidentally entered your body. While there is no evidence to suggest that MRI is harmful to unborn babies, as a precaution, the Department of Health advises against scanning pregnant women unless there is a clinical benefit. We do not test for pregnancy as routine so if you think you may be pregnant you should not take part in this study. As some of the scans are noisy, we would give you earplugs, head padding or headphones to make this quieter for you. Some people scanned in MRI scanners, especially 7 Tesla scanners, may experience a mild dizzy sensation as they are moved into the scanner. This is normal and the sensation starts to go away as soon as you are in the scanner.

It is important to note that we do not carry out scans for diagnostic purposes, and therefore these scans are not a substitute for a doctor's appointment. Our scans are not routinely looked at by a doctor; rather our scans are intended for research purposes only. Occasionally a possible abnormality may be detected. In this case, we would have the scan checked by a doctor. If the doctor felt that the abnormality

was medically important, you would be contacted directly and recommended to have a hospital (NHS) diagnostic scan arranged. All information about you is kept strictly confidential.
Although taking blood is a very safe procedure, it can be uncomfortable and may result in fainting, localised pain, or bruising. If you feel light-headed, we will position you comfortably on a bed. Any pain or bruising from the needle site should disappear in a few days.

What are the possible benefits of taking part?
You will not benefit directly from taking part in this study, but we hope that the information we get from this study will help to improve the treatment of musculoskeletal pain in the future.

Will I be reimbursed for taking part?
You will not receive any payment for taking part in this study. However, we will reimburse you for your travel and parking expenses.

Will my General Practitioner/family doctor (GP) be informed of my participation?
We will not routinely notify your GP if you decide to take part in this study as it will not affect your clinical care in any way. We may contact your GP to follow up any incidental findings that may come to light during the course of the study.

What will happen to the samples I give?
If you are selected for this component of the study, we will collect blood from you, and they will be stored in Laboratories of Oxford University. Your blood sample will be assigned a code and your data will also be identified only by this number. In the blood, we will determine the presence of inflammatory markers and their relationship between neuropathy and the risk to develop pain, and/or its severity. Because these tests are performed on a research basis and cannot predict the risk of developing pain on an individual basis you will not receive these results. If you agree to your samples being used in future research, your consent form will be held until the samples have been used up.

What will happen to the samples if I give permission for their use in future research?
We will ask for your permission to keep your anonymised samples beyond this study. This will be optional. Your anonymised samples will be used mainly by local researchers, ethically approved research projects may take place in hospitals, universities, non-profit institutions or commercial laboratories worldwide. All personal information that could identify you will be removed or changed before information is shared with other researchers or results are made public.

Will any genetic tests be done?
We may extract DNA from your blood to study a potential relationship of your genes with neuropathy and the risk to develop pain, and/or its severity. The DNA given to researchers will not have information that identifies you. However, your DNA is unique to you so it can never be completely anonymous.

Sometimes the genes that we inherit increase the risk of health conditions, for instance heart disease or rare forms of cancer. In people, whose risk is known to be higher than average, there is action that can be taken to reduce the risk of these conditions developing or causing problems in the future. In doing this research, it is possible that we may by chance find genetic changes in your sample that may increase the risk that you have of developing one of these conditions. This kind of genetic change is termed an incidental finding. You can decide whether or not you want to be informed about such medically actionable findings. If a medically actionable finding is identified and you opted to be informed, then a clinically qualified member of the research team will arrange an appointment with you to discuss the findings.

Will my taking part in the study be kept confidential?
Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. All information which is collected about you during the course of the research will be kept strictly confidential and coded, stored securely under the responsibility of Dr Anushka Soni. Your name and address will be removed from the information we collect as soon as it is possible to do so. All hard copies of the information will be stored in a locked filing cabinet within swipe and security code access at the Botnar Research Centre. Computerised data will be stored on a password protected, encrypted University of Oxford computer. Data collected online will be anonymised as soon as it is possible to do so

and stored on a password protected, secured university server: data are collected through a secured internet connection. The information will be stored for a period of 10 years and then will be destroyed securely.

Responsible members of the University of Oxford and the Oxford University Hospital NHS Trust may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations.

What will happen to my data?

Data protection regulation requires that we state the legal basis for processing information about you. In the case of research, this is 'a task in the public interest.' The University of Oxford, based in the UK, is the data controller and is responsible for looking after your information and using it properly.

We will be using information from you and your medical records in order to undertake this study and will use the minimum personally identifiable information possible. The local study team will use your name, NHS number, homes address, and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. The audio recording for the focus group will be deleted immediately after transcribing. We will keep identifiable information about you for up to 3 years after the study has finished. We will store the de-identified research data, transcript and any research documents with personal information, such as consent forms, securely at the University of Oxford for 10 years after the end of the study.

The videos of your movements will then be uploaded to a secure cloud-server, from where computer software will analyse the movements and covert the videos into stickman-like images. These will be stored in secure files and the original videos will be deleted.

Data collected by Sleepio (Big Health Ltd) will be stored (unless you request deletion) indefinitely, in their production data store hosted, at AWS (Amazon) in the United States. This data includes your name, email address, date of birth, study ID code and health information. All data is stored fully encrypted and complies with UK and European General Data Protection regulations. Upon signing up to Sleepio, you will need to agree to the privacy policy (https://www.sleepio.com/privacy/) and terms and conditions (https://www.sleepio.com/terms) which state the Big Health will act as Data Controller for these data and therefore will retain access to said data beyond the duration of the research study. Should you want your data to be deleted, you can submit a request to Big Health's Security, Privacy and Compliance Officer, as outlined in the Privacy Policy. Sleepio will delete the primary data source within 30 days, and it will circulate out of their logs and data backups within 6 months.

The researchers will have access to information that you enter into the Sleepio programme, including your name and email address, time joined, date of last login and current session status, sleep scores (from sleep diary inputs) and your case file which shows your Sleepio "to do" list and changes in sleep efficiency. Data sent from Sleepio to the researchers will be encrypted (password protected).

If you agree to your details being held for you to be contacted regarding future research, we will retain a copy of your consent form until such time as your details are removed from our database but will keep the consent form and your details separate. Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited in order for the research to be reliable and accurate. Further information about your rights with respect to your personal data is available at https://compliance.web.ox.ac.uk/individual-rights

You can find out more about how we use your information by contacting Dr Anushka Soni.

What will happen if I don't want to carry on with the study?

It is entirely up to you whether or not you would like to take part in this study. If you decide at any point that you no longer wish to take part, this will not affect the care you receive from the NHS in any way. If you withdraw from the study, we will use any data that we have already collected from you, but no further research assessments will need to be conducted.

What happens at the end of the study?

We plan to share the results of this study with the medical community by presenting it at conferences and publishing it in medical journals. It will not be possible to identify you individually from the information we publish. If you would like to know the results of the study once it has been completed, please contact Dr Anushka Soni.

What if there is a problem?
The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study. NHS indemnity operates in respect of the clinical treatment which is provided.

If you wish to complain about any aspect of the way in which you have been approached or treated, or how your information is handled during the course of this study, you should contact Dr Anushka Soni (01865 227 374, Anushka.soni@ndorms.ox.ac.uk) or you may contact the University of Oxford Research Governance, Ethics & Assurance Team (RGEA). RGEA email rgea.complaints@admin.ox.ac.uk.

The Patient Advisory Liaison Service (PALS) is a confidential NHS service that can provide you with support for any complaints or queries you may have regarding the care you receive as an NHS patient. PALS is unable to provide information about this research study. If you wish to contact the PALS team, please contact the Nuffield Orthopaedic Centre: 01865 221473, PALS@ouh.nhs.uk.

How have patients and the public been involved in this study?
Potential participants were involved in reviewing the Participant Information Sheet. In designing this study we have also taken into account patient opinions on the frequency of participant visits and the tests that we will carry out.

Who is organising and funding the study?
This study is being sponsored and funded by the University of Oxford.
None of the doctors or nurses involved in your clinical care are being paid for their role in the study.

Who has reviewed the study?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect participants' interests. This study has been reviewed and given favourable opinion by South Central - Oxford B Research Ethics Committee.

Participation in future research:
If you agree to be contacted regarding future research studies, your contact details would be held separately from this study on a password protected computer in the Botnar Research Centre. One of the research team would be the first to contact you and you can ask to be removed from the register at any time. You are not at all obliged to take part in any future research studies you are contacted about.

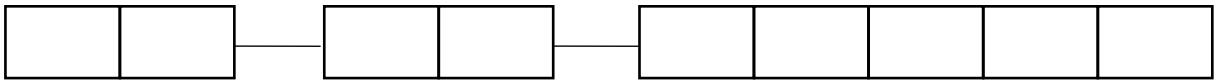
Further information and contact details:
Please contact Dr Anushka Soni by:
telephone on 01865 227 374
or email on anushka.soni@ndorms.ox.ac.uk

Thank you for reading this information.

D.3 PainLESS Study: Consent form

Dr Anushka Soni
Botnar Research Centre, Windmill Road, Oxford, OX3 7LD T: 01865 227 374
Anushka.soni@ndorms.ox.ac.uk

Study Code: *Site ID Code:* *Participant identification number:*



REMOTE CONSENT FORM

Title: Characterisation of **Pain** in patients with musculoskeletal disease: a prospective, **L**ongitudinal, observational study with an **E**mbedded feasibility window of opportunity **S**leep **S**tudy (Pain-LESS)

Name of Researcher:

Researcher to seek and record informed oral consent, after participant has had sufficient time to think about whether they want to take part.

Please check the boxes to record that the question has been asked by the researcher and that the participant has responded in the affirmative:

1) I confirm that I have read the D.2 dated _____ (version ___) for this study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.		
2) I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.		
3) I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from University of Oxford, from regulatory authorities and from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.		
4) I understand that this is a research scan that is not useful for medical diagnosis, and that scans are not routinely looked at by a doctor. If a concern is raised about a possible abnormality on my scan, I will only be informed if a doctor thinks it is medically important such that the finding has clear implications for my current or future health.		
	Yes	No
5) I agree to donate blood samples. I consider these samples a gift to the University of Oxford and I understand I will not gain any direct personal or financial benefit from them.		
	Yes	No

6a) I understand and agree that my samples will be used in research aimed at understanding the genetic and molecular influences on disease and that the results of these investigations are unlikely to have any implications for me personally.		
6b) I understand that the genetic analysis may identify results which are found by chance (incidental findings) and/or medically actionable (judged to be important for my health and can be acted upon medically). I wish to be informed about such medically actionable genetic findings.	Yes	No
7) If invited, I agree to take part in some online games.	Yes	No
8) If invited, I agree to be recorded whilst performing physio-type movements.	Yes	No
9) If invited, I agree to take part in an online sleep intervention with sleep monitoring.	Yes	No
10a) I understand that if I am invited to participate in a focus group, an audio recording will be taken of the focus group in which I participate.	Yes	No
b) I agree to my statements in the focus group being quoted in the write up of this study.	Yes	No
11) I agree to take part in this study.		
Additional:		
12) I agree to be contacted about ethically approved research studies for which I may be suitable. I understand that agreeing to be contacted does not oblige me to participate in any further studies.	Yes	No
13) I agree for my anonymised samples to be used in future research, here or abroad, which has ethics approval. I understand this research may involve commercial organisations.	Yes	No

_____
Name of Participant

_____ _____ _____
Name of Researcher taking consent Date Signature

**1 for participant (e.g. emailed securely to participant); 1 for researcher site file (original) ; 1 (to be kept in medical notes* (if participant is a patient).

D.4 PainLESS Study: MRI safety screening

3T VOLUNTEER MRI SCREENING FORM

Please carefully check the following as some items can interfere with MR or be hazardous to your safety. Mark your answer with a circle and add any relevant information. Safety calculations made by the scanner require us to input your weight, height and sex assigned at birth. **Your answers will be kept strictly confidential.**

Volunteer name _____ **Sex** _____

Date of birth _____ **Weight** _____ **kg** **Height** _____ **cm**

I understand these questions are used to determine if it is safe to take part in the study and may be looked at by designated individuals from the University of Oxford. If I am not scanned these details will be destroyed. If I am scanned these details will be securely stored for up to 5 years and then destroyed.

☐ *Please initial if you agree*

IF YOU HAVE ANY QUESTIONS THEN PLEASE ASK US BEFORE YOUR SCAN		
Do you have a heart pacemaker or pacing wires?	YES	NO
Have you had any heart surgery (e.g. coronary stent, heart valve replacement, PFO closure)?	YES	NO
Have you had any surgery to your head including eyes / ears / brain?	YES	NO
Have you had any surgery to your neck or spine?	YES	NO
Do you have any implanted devices (e.g. aneurysm clip, hydrocephalus shunt, nerve stimulator, cochlear implant, mesh)?	YES	NO
Have you had any operations involving metallic pins / plates / screws / wires?	YES	NO
Have you had any surgical procedures or endoscopy in the last 6 weeks? (Please write below)	YES	NO
Have you **ever** had any other surgical procedures of any kind, however minor or as a child? (Please write below)	YES	NO
Have you **ever** sustained any injuries involving metal to the eyes or other part of the body (e.g. from drilling, grinding or welding)?	YES	NO
Have you ever had a serious accident or injury (e.g. road traffic or industrial accident, explosion, shooting or shrapnel injury?)	YES	NO
Have you ever had a fit or blackout, or do you suffer from epilepsy or diabetes?	YES	NO
Do you have any of the following (if yes please circle):		
Body piercing, eye makeup, coloured contact lenses / Hearing aid, wearable medical device (e.g. drug pump, glucose monitor) / Dentures, dental braces, dental implant, dental bridge / Medicated skin patch (e.g. pain, HRT, nicotine, contraceptive)		
Tattoos (including cosmetic) / Artificial limb, prosthesis, splint, brace or support / IUD (contraceptive coil) If yes please state type:		
Could you be pregnant?	N/A / YES	NO
Are you wearing any clothing, including underwear, that contains metallic threads or has been silver impregnated (e.g. anti-microbial)?	YES	NO
Do you understand that this is a research scan and is not useful for diagnosis?	YES	NO
Have you removed your jewellery, hairgrips, hearing aids, watch, spectacles, keys and coins?	YES	NO

Volunteer / Guardian signature _____ **Date of study** _____

Screened by _____ **Signature** _____ **Consent sighted** _____

D.5 PainLESS: Description of questionnaires

Participants completed a series of validated questionnaires assessing pain, medical history, cognition, sleep, mood, physical activity, and quality of life using REDCap, a secure web-based survey tool. These assessments were conducted at baseline prior to randomisation, and at follow-up intervals of 3-, 6-, and 12-months post-randomisation. Given the close relationship between pain, mood, and anxiety, several measures of emotional well-being were included.

D.5.1 Demographics and medical history

Demographic information collected included age, sex assigned at birth, handedness, self-reported ethnicity, educational attainment (years in full-time education, and highest educational qualification), and employment status. Medical history encompassed the duration of fibromyalgia symptoms, the date of diagnosis (to the nearest month/year), current and previous treatments for fibromyalgia, and other medical conditions.

Participants were asked about specific analgesic medications commonly used in fibromyalgia, including paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, amitriptyline, gabapentin or pregabalin, and duloxetine. These medications are frequently prescribed to manage fibromyalgia-related pain due to their varied mechanisms of action. Space was also provided to enter free text for drugs not in that list.

Participants rated how much pain relief analgesia medications provided on a scale of 0 (no relief) to 100 (complete relief). During the in-person assessment, participants were again asked about the same analgesia medications, and asked how many hours previously they had last taken a dose.

Understanding participants' medical history, especially analgesia use, is crucial for assessing potential confounding factors related to medication use that may influence pain perception or cognitive function[326].

Lifestyle factors such as alcohol and tobacco use were recorded. Additionally, height and weight were measured during the baseline study visit.

D.5.2 Pain & pain-related questionnaires

D.5.2.1 Pain Numeric Rating Scales

The numeric rating scale (NRS) provides a simple yet effective method for patients to rate pain intensity. The NRS demonstrates high validity compared to other pain measures, and good test-retest reliability[196]. A 0–100 scale (no pain at all to worst pain) was used during in-person assessments to capture more nuanced variations in pain severity at a given moment, whereas the 0–10 scale in online assessments aligns with the PainDETECT questionnaire (described below) for retrospective reporting of pain over time.

During the in-person assessments, participants were asked to rate “how severe is your pain right now”, and “how severe do you think your pain will be in 3 months’ time”.

Appendix D

On the online questionnaire, participants rated the severity of their pain at the current moment, the strongest pain in the past 4 weeks, and the strength of their pain on average in the past 4 weeks. This NRS formed part of the PainDETECT questionnaire, described below, but does not form part of the scoring system.

D.5.2.2 Fibromyalgia Impact Questionnaire Revised (FIQR)

The FIQR served as the primary clinical endpoint of the study. It is a validated tool based on the revised symptom impact questionnaire (SIQR) used in rheumatology, and assesses the impact of fibromyalgia on an individual's daily life[43]. It includes questions on the following domains: physical functioning, pain intensity and characteristics, fatigue, sleep quality, emotional well-being (mood and anxiety), and impact on work and social interactions.

D.5.2.3 Fibromyalgia Survey Criteria

The 2016 American College of Rheumatology Fibromyalgia Survey Criteria is a set of diagnostic guidelines for fibromyalgia[499]. It consists of two domains, the symptom severity scale (SSS), and widespread pain index (WPI). The SSS evaluates severity of key symptoms in fibromyalgia, including poor sleep, brain-fog, fatigue, low mood, and somatic symptoms such as headaches and abdominal pain. The WPI measures self-reported pain in a set of 19 specific body regions where has been experienced in the past week. The WPI and SSS not only confirm fibromyalgia diagnosis but also provide a framework for measuring the intensity and distribution of nociplastic pain, a key

mechanism in fibromyalgia. These metrics serve as both diagnostic tools and indicators of disease progression[230; 502].

D.5.2.4 PainDETECT questionnaire

The PainDETECT questionnaire assesses the presence and severity of neuropathic pain[166]. Key features of pain examined include pain characteristics (e.g. burning, tingling, electric shocks), intensity, pattern (constant versus intermittent), and additional sensory symptoms such as numbness or temperature sensitivity which are features of neuropathic pain. Although PainDETECT was originally designed for neuropathic pain, it is also valuable in fibromyalgia because of the overlap with nociplastic pain mechanisms, which share features like sensory hypersensitivity and altered pain processing.

D.5.2.5 Central Sensitisation Inventory (CSI)

The CSI assesses symptoms associated with central sensitisation, thought to be a key mechanism underlying fibromyalgia[295]. It consists of 25 items evaluating a range of physical and emotional symptoms, such as widespread pain, fatigue, sleep disturbances, emotional wellbeing, and sensitivity to stimuli such as light, noise and odours.

D.5.2.6 Pain Catastrophising Scale (PCS)

The PCS is a 13-item questionnaire which measures the degree to which an individual experiences negative thoughts and feelings about pain[438]. The three principal components are rumination (persistent thoughts about pain), magnification (exaggerating the threat of pain), and helplessness (feeling powerless to manage pain). Pain catastrophising is associated with higher pain perception and worse disability with a score of ≥30 representing clinically significant catastrophising behaviour[439].

D.5.2.7 Chronic Pain Acceptance Questionnaire (CPAQ)

The CPAQ provides a measure of how much individuals accept their pain and engage in activities despite it[298]. Higher acceptance of pain is associated with better psychological and physical outcomes.

D.5.3 Health-related Quality of life

D.5.3.1 Short-form 36 Health Survey

The SF-36 health survey assesses overall health and wellbeing across eight domains[163]: physical functioning, role limitations due to physical health, role limitations due to emotional wellbeing, fatigue, emotional wellbeing, social functioning, pain, and general health. In this study, the Bodily Pain subscale (BPS) is used as a measure of the impact of pain on physical health. It is a composite of two items measuring pain intensity and pain interference, a measure of how much pain interferes

with daily activities. Scores for each subscale are transformed to a scale of 0-100, with lower scores representing worse health status.

D.5.3.2 EuroQoL EQ-5D-5L

The EuroQoL EQ-5D-5L is a standardised measure of health-related quality of life. It consists of five dimensions of health (5D), each rated on five levels of severity (5L): mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. A country-specific weighting can be applied to derived quality adjusted life years (QALY).

D.5.4 Cognition

D.5.4.1 British Columbia Cognitive Complaints Inventory (BC-CCI)

The BC-CCI assesses subjective cognitive complaints through six items assessing self-reported problems over the past seven days with concentration, memory, expressing thoughts, word finding, thinking speed, and problem-solving[214]. Although more typically used in evaluation of patients with mood disorders, this outcome measure was selected for this study to facilitate comparison with the SPIN trial[253], which evaluated the effect of dCBTi on cognitive function in patients with insomnia.

D.5.5 Sleep quality

D.5.5.1 Insomnia Severity Index (ISI)

The ISI assesses severity of insomnia symptoms and their impact, and is a widely used measure of insomnia severity in both clinical and research settings[31]. It consists of seven items evaluating different aspects of insomnia, including difficulties with falling asleep, staying asleep, and waking up early; satisfaction with current sleep patterns; interference with daily functioning; quality of life; worry about sleep problems.

D.5.5.2 Pittsburgh Sleep Quality Index (PSQI)

The PSQI assesses sleep quality and patterns. It complements the ISI by providing an assessment of overall sleep quality and including aspects such as sleep duration, time in bed, sleep latency, sleep efficiency, and use of sleep medications[69].

D.5.6 Physical activity and fatigue

D.5.6.1 Chalder Fatigue Scale (CFS)

The CFS measures the severity of fatigue impact on daily functioning[78]. It encompasses both physical fatigue (e.g. tiredness after activities), and mental fatigue (e.g. cognitive difficulties).

D.5.6.2 Tampa Scale of Kinesiophobia (TSK)

The TSK assesses fear of movement due to the belief that physical activity may cause further harm, which can hinder recovery in chronic pain[310].

D.5.6.3 International Physical Activity Questionnaire (IPAQ) – Short form

The IPAQ evaluates self-reported physical activity in the previous seven days, and covers time spent performed four types of activity[107]: vigorous activity, moderate activity, walking, and sedentary behaviour. From these, metabolic equivalent of task (MET) can be derived, and individuals can be categorised into three levels of physical activity: low, moderate, and high.

D.5.7 Emotion and reward-responsiveness

Emotional and motivational factors significantly impact the experience and management of chronic pain, especially in fibromyalgia[159; 356]. Dysregulated reward systems can influence how individuals cope with pain, and pain itself can alter reward sensitivity, making BIS/BAS scales vital in understanding the interplay between pain and motivation.

D.5.7.1 Behavioural Inhibition and Activation System Scales (BIS/BAS)

These scales assess two motivational systems that regulate behaviour: the behavioural inhibition system (BIS) which measures sensitivity to punishment and avoidance of

negative outcomes, and the behavioural activation system (BAS) which measures sensitivity to reward and motivation towards achieving positive outcomes[75]. The BAS is divided into three components: drive, fun-seeking, and reward responsiveness. Motivational style plays a role in determining pain outcomes as pain relief is a form of reward, and thus measures of motivational behaviour is relevant for interventional studies in chronic pain[263; 481].

D.5.7.2 Patient Health Questionnaire 9 (PHQ-9)

The PHQ-9 is a widely used screening tool for depression, consisting of nine items corresponding to the diagnostic criteria for major depressive disorder[248]. The score on the questionnaire is a measure of symptom severity.

D.5.7.3 General Anxiety Disorder 7 (GAD-7)

The GAD-7 is a common tool used to screen for anxiety symptoms, consisting of seven items relating to the core anxiety symptoms including feeling nervous, inability to stop worrying, and difficulty relaxing[430]. The total score provides a measure of anxiety symptom severity.

D.5.8 Adverse events

At follow-up, participants reported any potential adverse events related to dCBTi, including physical and psychological symptoms such as fatigue, low mood, pain, and

difficulty concentrating. They rated the severity of these symptoms and how much they interfered with normal functioning, on a scale from "Did not experience" to "Very much." Participants also reported incidents of sleepiness over the preceding 3 months, including hospital admissions, accidents, falls, or near-miss incidents, and had the opportunity to mention any other relevant events.

D.5.9 Healthcare resource utilisation

For a planned economic evaluation, participants reported their healthcare service use over the previous 3 months, including hospital visits, medical imaging, and consultations with healthcare professionals (e.g., GPs, nurses, physiotherapists). Information was also collected on medications, unpaid caregiving, social services, and the financial impact of the condition on relatives and friends, including out-of-pocket expenses for care, transportation, and medical treatments.

D.6 PainLESS: Quantitative Sensory Testing (QST) protocol

During the in-person assessments, participants underwent an abbreviated quantitative sensory testing (QST) based on an established protocol developed by Rolke and the German Research Group on Neuropathic pain[375; 376]. QST is a technique used to determine skin sensitivity to thermal, touch, and vibration stimuli. It is a validated method for assessing sensory function and detecting abnormalities in pain processing, such as central sensitisation, which is often present in fibromyalgia patients. In this

trial, testing was conducted over a central (sternum) and peripheral body site (dorsum left hand). Three experimental pain models were evaluated: mechanical pain threshold (MPT), wind-up ratio (WUR), and pressure pain threshold (PPT).

D.6.1 Mechanical Pain Threshold (MPT)

A set of standardised punctate probes were used, and the force (in millinewtons, mN) that a participant first reported “sharp touch” was recorded.

D.6.2 Wind-up Ratio (WUR)

For WUR, the same devices were used. Repeated stimuli were applied to assess temporal summation of pain, a process whereby repeated stimuli may increase pain sensitivity. The ratio between the pain rating for the final and the initial stimulus is the wind-up ratio (WUR). As there was considerable between-subject variability in reported pain in fibromyalgia patients in the observational cohort, this introduced challenges in stimulus selection. Since a nociceptive stimulus that is non-painful in one individual may be intolerable in another, it makes stimulus selection challenging. Furthermore, ratings may be affected by a ceiling effect if the initial stimulus is perceived to be very painful[3]. To address these limitations, perception locking of the stimulus was applied. In this method, the stimulus is adapted to a defined subjective pain rating for each individual. In this trial, the initial stimulus applied was 128mN, and the intensity was increased or reduced to achieve an average rating between 2 and 4 out of 10 on the

dorsum of the right hand over three stimuli. As thresholding can change over time due to individual variability over time, thresholding was re-applied during the follow-up visit.

D.6.3 Pressure Pain Threshold (PPT)

PPT measures the sensitivity to mechanical pressure, providing insight into hyperalgesia. PPT was assessed using a pressure algometer (Wagner instruments). Pressure was applied over the two body sites and the pressure (in mN) at which patients first noticed pain was recorded.

D.7 PainLESS: MRI Protocol

FMRIB 3T MRI Scanning Procedure
Study: 2023_006 – FM Sleepio

Related Documents and Location

2023_006 NRES Application (electronic, study docs folder)
2023_006 NRES Approval Letter (electronic, study docs folder)
2023_006 Study Protocol (electronic, study docs folder)
2023_006 PIS and Consent Form (electronic, study docs folder)

Study Information

Study Title: Characterisation of **Pain** in patients with musculoskeletal disease: a prospective, **L**ongitudinal, observational study with an **E**mbedded feasibility window of opportunity **S**leep **S**tudy (PAIN-LESS)

Study Group: Pain and Anaesthetics

PI: Anushka Soni

Calpendo ID: 2023_006 – FM Sleepio

Ethics Number: 19/SC/0168 (NRES)

Introduction: This is a feasibility study for a randomised controlled trial of digital cognitive behavioural therapy for insomnia (dCBT), *Sleepio*, vs standard care in patients with fibromyalgia. This is a sub-study of an observational study which is currently running. Eligible and consenting participants will undergo a baseline assessment which will include neuroimaging. Following this they will be randomized to a 12-week treatment course of either Sleepio or standard care. At the end of the treatment period, participants will be asked to attend for a follow-up visit which will again include neuroimaging. We plan to investigate the impact of Sleepio on structural and functional neuroimaging changes in patients with fibromyalgia.

General Info: 40 out-patient participants with fibromyalgia, aged 18 years and over, will be scanned on 2 occasions.

Scanner: 3T

Category: Category 2 - Vulnerable subjects or low risk intervention

Staffing levels: 1 x advanced scanop and 1x specifically trained researcher

Session Time: 60min TBC

Incidental Findings Procedure:

Joint SOP Dealing with Research Neuroimaging Incidental Findings (OHBA_014_V1, FMRIB_002_V5, Neuro_002_V5)

Researchers and their contact details

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Other Team Members

AW
Research Assistant
Wellcome Centre for Integrative Neuroimaging
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Equipment Required

Standard

32 Channel Head Coil
Regular mirror
Ear plugs
Immobilization sponges
Buzzer

Lighting and stimulus

Bore lights on
Room lights on
LCD on

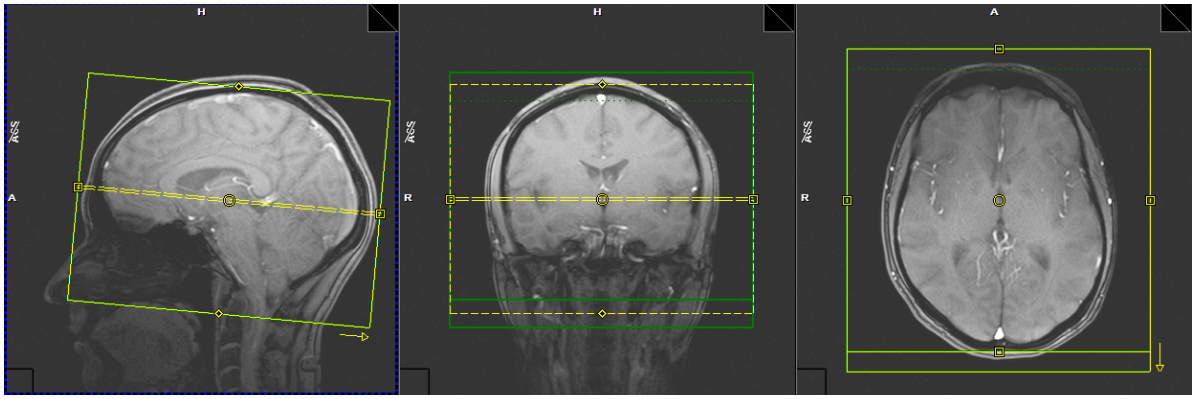
Ancillary

Biopac respiratory bellows
Biopac pulse meter

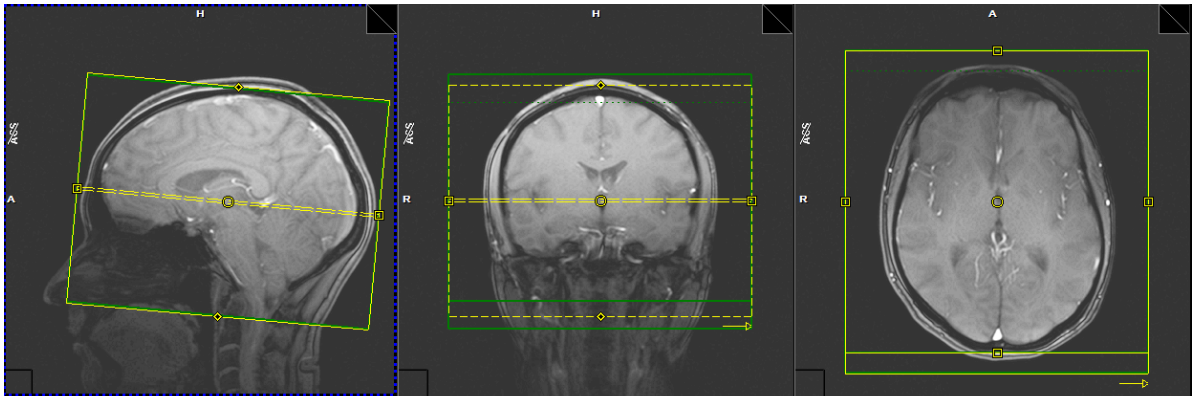
Protocol Sequences

USER >> FMRIB User >> 2023_006 Sleepio >> Protocol v1

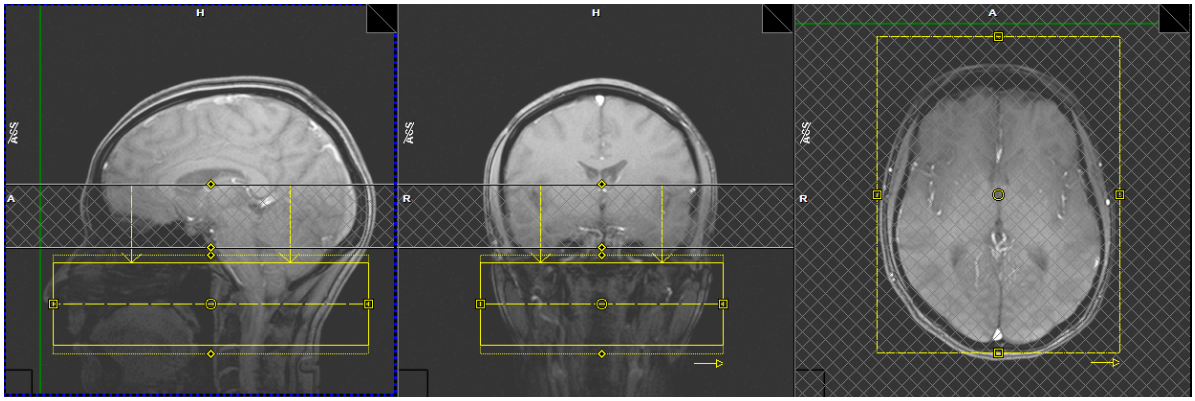
1. **localiser_3plane_32ch**
   14s
   - Auto-runs, no setup required
2. ***– RS fMRI –***
3. **bold_mbep2d_2mm_MB6_v2_RS**
   10m11s
   - Axial orientation, angle to ACPC, straighten on coronal if required
   - Cover whole brain
   - Open adjustments, click the 3D Shim tab and do 3x manual shims (ie Measure, Apply (top), Calculate, Apply (bottom))
   - Resting state instructions: “Look at the cross for the next scan, blink normally and try not to fall asleep.”



4. ***– Copy Adj Vol from BOLD –***
5. **fieldmap_gre_2mm_mb**
   1m34s
   - Auto-copies COSG&SR from bold_mbep2d_..._RS
   - Need to manually copy the adjust volume from bold_mbep2d_..._RS
   - Click “OK” on the Copy Reference Parameter Conflict prompt

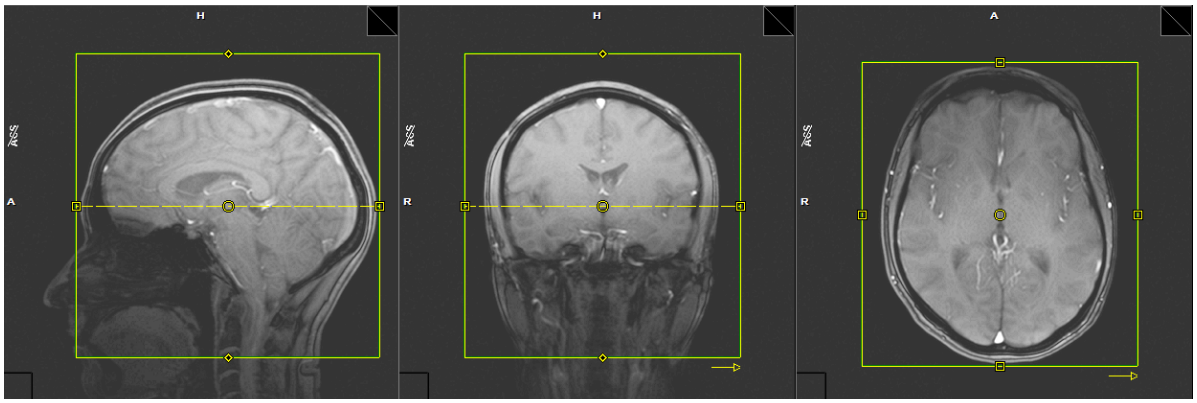


6. **TOF_3D_neck_quick**
   42s
   - True axial orientation, don’t angle or straighten
   - Position to cover from C2/C3 to lower cerebellum
   - Once completed load into the viewer and find the best slice between vessel loops e.g. F70

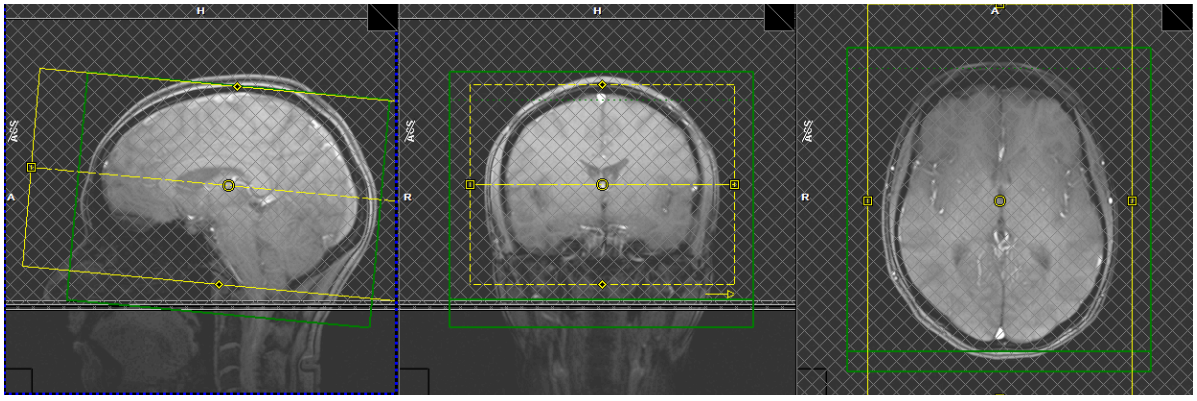


7. **t1_mpr_ax_1mm_iso_32ch_v2**
   5m31s
   - True axial orientation, do not angle or straighten (used for spectroscopy planning)
   - Cover whole brain

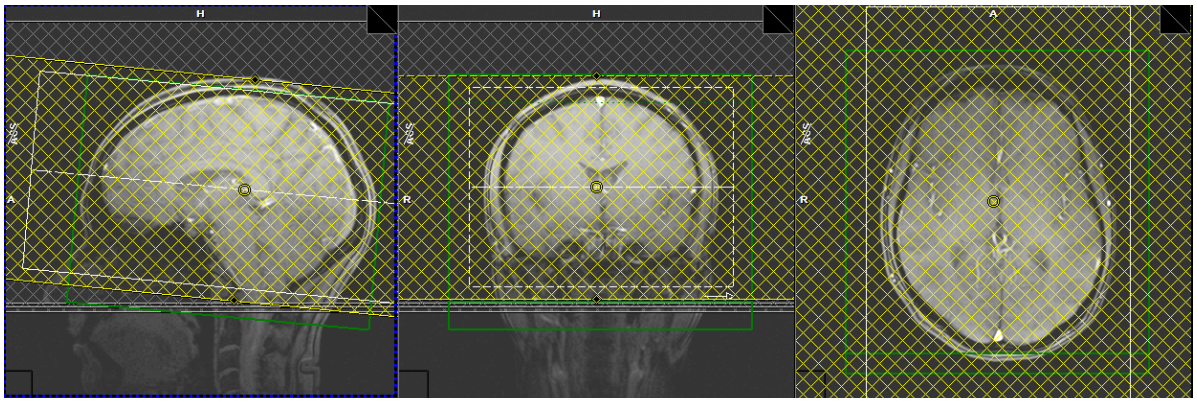
   - Once acquired use 3D package to re-slice into Ax/Cor/Sag 1/1mm slices (use 1mm pre-set)
   - Load into planning segments in the order Sagittal, Coronal, Axial (left to right)



8. ***– ASL –***
9. ***– Turn off coupled graphics –***
   - Make sure that Coupled Graphics are off before planning the ASL (Tools – Coupled Graphics OFF)
10. ***– Copy Adj Vol from BOLD –***
11. **jw_tgse_PCASL_Hybrid_multiTI_PLD1_LR_LowRes**
    2m18s
    - Position slice slab and Adj Vol
      - Axial orientation, angle to ACPC, straighten on coronal if required, cover from the cerebellum up (don't go any lower then you need to)
      - Copy Adj Vol from bold_mbep2d_2mm_MB6_v2_RS

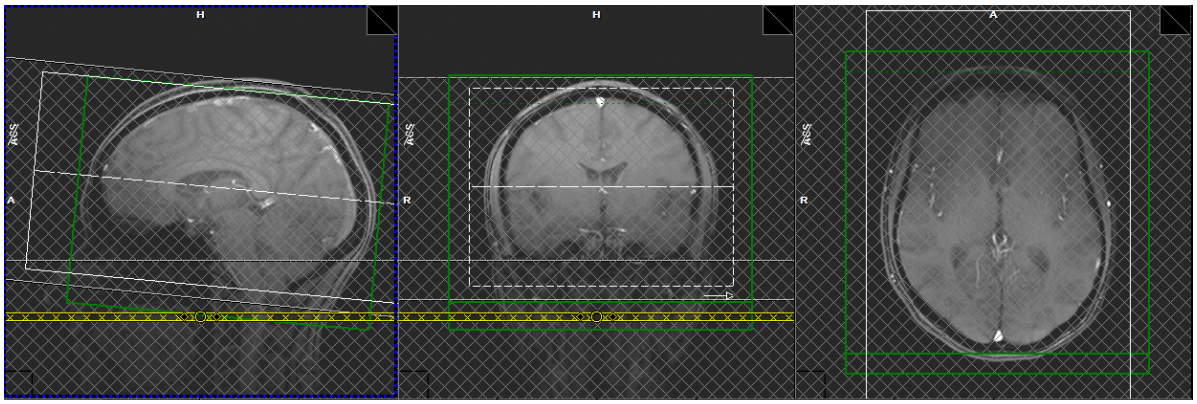


- Adjust Sat region 1 to match imaging slab
    - Go to the Geometry Tab, select the Saturation Sub-Tab, choose Sat. region 1 and centre and angle to cover the scan volume

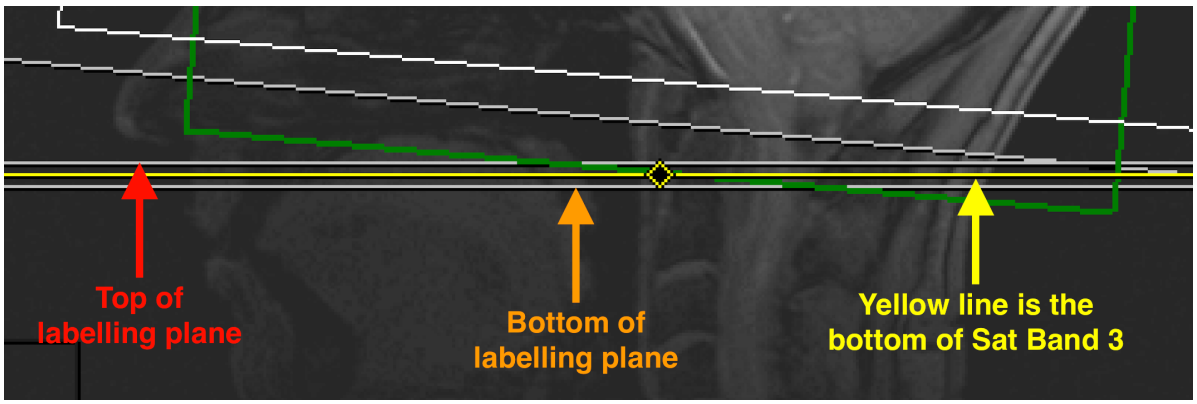


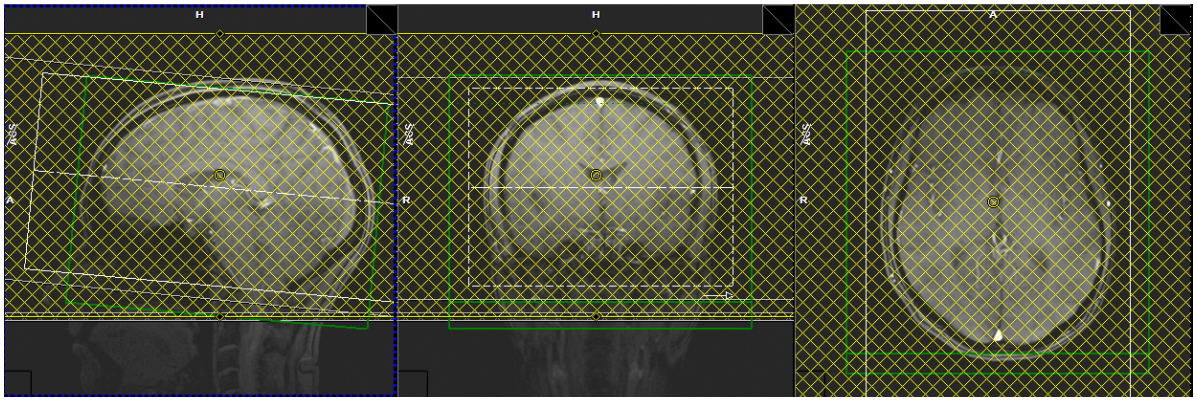
- Go to the Geometry Tab, select the Saturation Sub-Tab, choose Sat. region 1 and centre and angle to cover the scan volume

- Enter the labelling plane
    - Select Sat. region 2 and click the … button, input the height chosen above, eg F76.8 and click enter in the centre of XX box
        - Sometimes this will display in “shift” mode, in which case just enter your labelling plane location, adding a minus sign if it is inferior of isocentre (e.g. for F52 enter -52)
        - If it is in “L-P-H” mode enter the labelling plane location in the third box. If the current setting is superior of isocentre (e.g. H12) and you want it to be inferior (e.g. F52) then enter a minus sign first (e.g. -52) and you should see the H change to an F.
    - NB do not angle Sat region 2



- Setup up the ???? saturation band
  - Select Sat. region 3 and position it so that the bottom of the Sat band lies in the middle of the labelling plane





- Resting state instructions: “Look at the cross for the next scan, blink normally and try not to fall asleep.”

12. – Copy Adj Vol from BOLD –

13. jw_tgse_PCASL_Hybrid_multiTI_PLD2_LR_LowRes
2m31s

- Auto-copies COSG&SR from jw_tgse_PCASL_..._LowRes
- Need to manually copy the Adj Vol from tgse_PCASL_..._LowRes

14. – Copy Adj Vol from BOLD –

15. jw_tgse_PCASL_Hybrid_multiTI_PLD3_LR_LowRes
2m37s

- Auto-copies COSG&SR from jw_tgse_PCASL_..._LowRes
- Need to manually copy the Adj Vol from tgse_PCASL_..._LowRes

16. – Copy Adj Vol from BOLD –

17. jw_tgse_PCASL_M0_LR_LowRes
44s

- Auto-copies COSG&SR from jw_tgse_PCASL_..._LowRes
- Need to manually copy the Adj Vol from tgse_PCASL_..._LowRes

18. – Spectro –

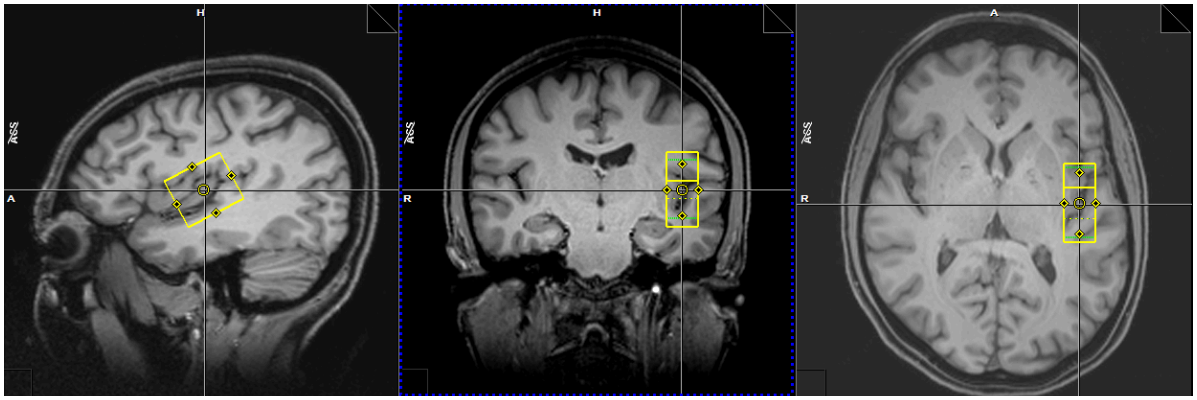
19. – Screenshot –

- If a return visit use previous screenshot to match positioning
- Otherwise take a screenshot of voxel location (Ctrl + Prt Scr, paste into Paint, save as) showing voxel location centred in each plane
- Save to Z: / _Study_Data / 2023_006 – FM Sleepio / 2023_006_XXX / 2023_006_XXX.png

20. mega_press_lw

15s

- Position the voxel over the left insula (researcher will advise), do not click apply yet



- SVS Shim Step 1
  - Select the '3D shim' tab
    - Click 'Measure', 'Calculate' and the **middle 'Apply'**
  - Select the 'Frequency' tab
    - Click 'Go' until you get a 'Y' in the 'Converged' column AND the difference in frequency is within ±10Hz
- SVS Shim Step 2
  - Select the '3D shim' tab
    - Click 'Measure', 'Calculate' and the **middle 'Apply'**
  - Select the 'Frequency' tab
    - Click 'Go' until you get a 'Y' in the 'Converged' column AND the difference in frequency is within ±10Hz
- SVS Shim Step 3
  - Select the '3D shim' tab
    - Click 'Measure', 'Calculate' and the **middle 'Apply'**
  - Select the 'Frequency' tab
    - Click 'Go' until you get a 'Y' in the 'Converged' column AND the difference in frequency is within ±10Hz
- Click close
- Click apply and run the measurement

21. – Check Line Width –

- Once the measurement has completed, load the mega_press_lw_V1 scan into the 'Spectroscopy' application (NB you may need to open the package from the 'Applications' menu)

- From the ‘Protocols’ menu, select open and then select ‘water_lw’, this will display a line width in Hz on the spectrum
- If this frequency exceeds 10Hz you will need to adjust voxel location and repeat all the above steps

22. mega_press_fa_cal

35s

- Auto-copies Measurement Parameters and AdjVol from mega_press_lw_V1
- Open inline display, the optimum transmit voltage is the max value, this should be used for all measurements for this voxel
- Make a note of the Tx voltage

23. – Update Tx Voltage –

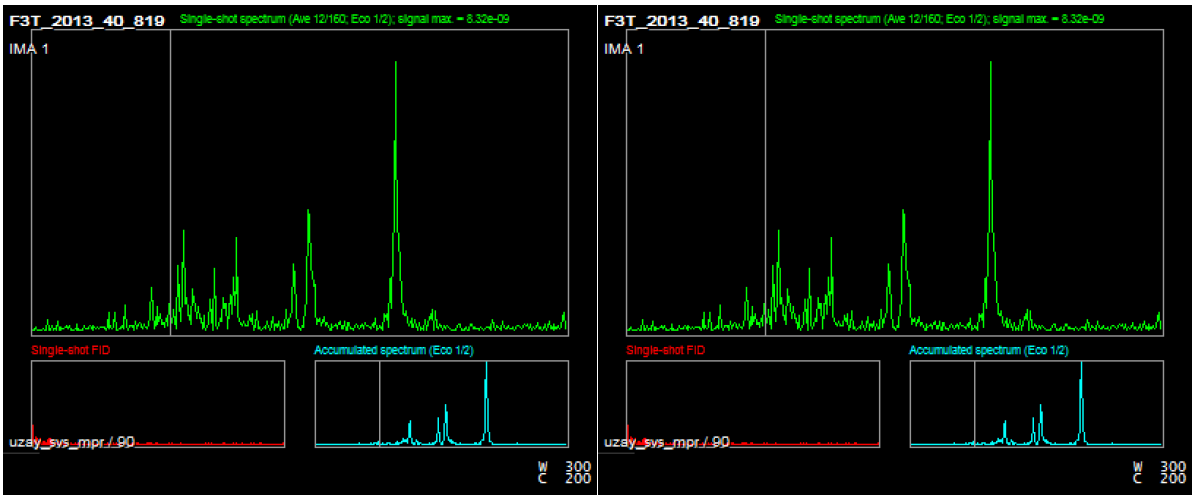
- When the sequence is active go to ‘Options’ then ‘Adjustments’
- Select the ‘Transmitter’ tab and update the Tx value from the previous scan

24. mega_press_TR1500_Acq

8m13s

- Auto-copies Measurement Parameters and AdjVol from mega_press_lw_V1
- Open adjustments, select transmitter tab, and enter optimum transmit voltage from the **mega_press_fa_Cal** sequence
- MRS instructions ”TBC.”

- NB 2 types of spectra will alternate, one with NAA and one with NAA suppressed



25. mega_press_wref1

15s

- Auto-copies Measurement Parameters and AdjVol from mega_press_lw_V1

26. mega_press_wref3

15s

- Auto-copies Measurement Parameters and AdjVol from mega_press_lw_V1

27. !!! Copy TWIX data !!!

- Once the study has completed and no scans are active copy the spectra to the 3T remote drive
- Open TWIX and save all sequences starting with mega_ to Z: / _Study_Data / 2023_006 – FM Sleepio / 2023_006_XXX /

Post Scan

- Copy spectroscopy data to the TWIX drive
- Researcher must confirm that the TWIX has been copied before leaving control room
- Researcher to retrieve all data from remote drive within 7 days (can be deleted after this point)
- Researcher to return stimulus equipment to default state

Researcher Acknowledgement

Use of limited release sequences

The use of limited release sequences entails a risk that they will crash or otherwise slow down a session.

It is important to note that in the case where there is a delay caused by these sequences you may be required to cut other scans in order to finish within your allocated time.

Responsibility for copying TWIX data

TWIX data (eg spectroscopy raw files and screenshots) stored on http://twix.fmrib.ox.ac.uk/ must be downloaded within 7 days of the scan session.

After this time the data may be deleted without warning.

D.8 PainLESS: Focus Group Questions

Information area	Example questions and prompts	Logic behind the questions
Introduction	Can you introduce yourself please and describe your background?	The question is to get respondents talking and feeling comfortable.
	How did you find out about the study, and what prompted you to take part?	This helps to understand the motivation and context for participants joining the study.
Initial Working Theory (IWT) 1: Study participants were motivated by a desire to improve care for fibromyalgia by taking part in research		
Motivation for being involved with research	What motivated you to be involved with this research?	To explore participants' motivations and understand the underlying reasons for their involvement.
	Did you hope to gain anything specific from participating?	To identify personal goals and expectations from the study.
Experience of being in a research study	What has your overall experience of being in this research study been like?	To gather general feedback on their participation experience.
	Have you participated in other research studies before? If yes, how does this compare?	To compare their current experience with past research involvement, if any.
Initial Working Theory (IWT) 2: Study participants prefer a mix of online and in-person assessments		
Preference for online vs in-person visits	Do you have a preference for online or in-person study visits? Why?	To understand participant preferences for study visit formats.
	How did you find the balance between online and in-person assessments in this study?	To evaluate if the current balance was effective and satisfactory.
Initial Working Theory (IWT) 3: Online assessments are perceived as less burdensome but may be more confusing compared to in-person assessments		

Appendix D

Information area	Example questions and prompts	Logic behind the questions
Online assessments	How did you find the length and complexity of the online assessments?	To assess the burden and user-friendliness of online components.
	Were there any particular online assessments that you found difficult or easy?	To gather detailed feedback on specific online assessments.
Initial Working Theory (IWT) 4: In-person assessments provide valuable interaction but can be burdensome for participants with chronic pain		
In-person assessments	How did you find the length and burden of the in-person assessments?	To evaluate the impact of in-person assessments on participants.
	Were there any aspects of the in-person assessments that stood out to you as particularly good or bad?	To collect specific feedback on in-person assessments.
Initial Working Theory (IWT) 5: The control intervention (sleep hygiene advice) is perceived as less effective than the active intervention (Sleepio)		
Usefulness of control intervention (for control group)	How useful did you find the sleep hygiene advice provided to the control group?	To understand the perceived effectiveness of the control intervention.
	Did you adopt any of the sleep hygiene advice? If yes, which ones?	To explore the practical impact and adoption of sleep hygiene advice.
Initial Working Theory (IWT) 6: The Sleepio intervention is effective but may have usability issues for participants with fibromyalgia		
Usefulness of sleep therapy intervention (for Sleepio group)	How did you find using the Sleepio app?	To gather feedback on the Sleepio app from the intervention group.
	Was there anything you found particularly difficult with the Sleepio app?	To identify specific challenges with the app.
	Do you think you might have preferred using a different modality for the program (e.g., phone/laptop)?	To assess preferences for different modalities of delivering the intervention.
	How motivated were you to stick with the program?	To understand participant engagement and motivation levels.

Appendix D

Information area	Example questions and prompts	Logic behind the questions
	Do you feel like it helped? Have you noticed a change?	To evaluate the perceived effectiveness of the Sleepio intervention.
	Did you learn anything new about the way we sleep?	To identify any educational benefits of the intervention.
	What was your favourite thing about the app?	To gather positive feedback and identify strengths of the app.
	What was your least favourite thing?	To identify areas for improvement in the app.
	Do you think any problems you found with the app were specifically related to your fibromyalgia?	To explore if fibromyalgia symptoms influenced their experience with the app.
Suggestions for improvement	Would you suggest anything to change within the app to make it better or easier to use?	To gather suggestions for improving the app.
	Did you use all the functions: diary, checklist, etc.? If so, were they easy to use/helpful? If not, why not?	To assess the usability and helpfulness of different app functions.
	Did you use the library articles or community?	To understand the extent of engagement with additional app features.
Future suggestions		
Suggestions for future research studies	Do you have any suggestions for how we can improve future research studies?	To gather participant feedback for enhancing future research efforts.
	If you could change one thing about the way this study was conducted, what would it be and why?	To gather insights into the most critical areas for improvement.
	How did you find the communication and support provided by the research team?	To evaluate the effectiveness of communication and support, and gather suggestions for improvement.

Appendix D

Information area	Example questions and prompts	Logic behind the questions
	Were the instructions and information provided throughout the study clear and helpful? How could they be improved?	To assess the clarity of study materials and gather suggestions for making them more user-friendly.
	Did you feel adequately informed and prepared for each stage of the study? How could we improve this?	To ensure that participants feel well-prepared and informed, and to gather suggestions for better preparation.
	How can we make the online assessments more engaging and less burdensome?	To gather specific suggestions for improving the online assessment experience.
	What would make the in-person assessments more convenient or comfortable for you?	To gather ideas for making in-person assessments more participant-friendly.
	Are there any additional resources or support that you think would have been helpful during the study?	To identify additional support needs that could enhance the participant experience.
	How can we better accommodate the needs of participants with chronic pain or other health conditions?	To ensure that future studies are more inclusive and accommodating of participants' health conditions.
	How can we make the study results more accessible and useful for participants?	To ensure that participants can benefit from the study results and to gather suggestions for better dissemination.
	What would motivate you to participate in future studies?	To identify key motivators that can help in designing future studies that attract and retain participants.
	Are there any incentives or rewards that you think would be appropriate and motivating for study participants?	To gather ideas on incentives that could enhance participant motivation and engagement.

Supplementary Table 1. Overview of topics and questions to be covered in focus group

D.9 PainLESS: Draft Statistical Analysis Plan

In anticipation of the trial being completed in the middle of 2025, I have formulated a statistical analysis plan, which is outlined below. This will be published in advance of unblinding analysis.

D.9.1 Populations and subgroups to be analysed

D.9.1.1 Populations

Intention to Treat (ITT): The primary analyses will be conducted on an ITT basis, ensuring that all randomised participants are included in their originally assigned groups regardless of adherence to treatment.

Per protocol (PP): All randomised subjects who completed the treatment period (12 weeks). This will be a sensitivity analysis to evaluate whether the pattern of missing data affects outcomes.

Protocol deviations will be described in the results section of the manuscript. These will include participants in the intervention group who do not use Sleepio (defined as not accessing at least one session of the programme), and participants in the control group who access Sleepio or a similar CBT-I programme outside the trial. For the primary ITT analysis, they will be analysed in the group they were randomised to.

A trial profile of participants will be presented as per CONSORT guidelines, and baseline characteristics will be presented stratified by group allocation. No significance testing will be performed between the groups at baseline[11]. Any imbalances in a randomised trial are, by definition, due to chance rather than systemic bias, and thus any significant findings are false positives[405].

D.9.1.2 Pre-specified Subgroups

Insomnia with objective short sleep duration: There is evidence that patients with insomnia with *objectively* short sleep duration (<6 hours) may respond differently to CBT-I[26; 471]. For this subgroup analysis, randomised participants with be subdivided into two groups: those with objective total sleep time (TST) <6 hours measured on actigraphy, and those with 6+ hours TST on actigraphy.

Severe insomnia: Randomised subjects will be divided into groups according to insomnia symptoms severity using validated cut-offs for the ISI: 0-7 no clinically significant insomnia. 8-14 subthreshold insomnia. 15-21, moderate clinical insomnia. 22-28, severe clinical insomnia. Given the small numbers likely to be present in the 'no clinically significant insomnia' group, this will be merged with the 'subthreshold insomnia' group, grouping participants with scores 0-14 together.

Responders vs non-responders: In the neuroimaging sub-study, participants in the intervention arm who achieve the MCID in FIQR (a 14% reduction in score[42]) will be classified as responders. Within the intervention group, neuroimaging will be used to identify predictors of response. This will be an exploratory analysis.

D.9.2 Analysis

All outcomes will be presented using descriptive statistics. The mean and SD will be presented for normally distributed variables, and the median and interquartile range for skewed variables. Continuous variables will be analysed in their raw form. Categorical and binary variables will be presented as counts and proportions. Standard errors and

Appendix D

95% confidence intervals will be reported for all primary and secondary analyses. All p-values will be two-sided. R v4.2.0 will be used for all analyses. All analyses will adhere to CONSORT guidelines[316]. Below I describe the analyses of the pre-specified primary and secondary outcomes, as registered on clinicaltrials.gov (ref: **NCT05962138**):

D.9.2.1 Primary Outcome

As outlined in this chapter, the sole primary outcome will compare intervention groups (Sleepio vs sleep hygiene) on their mean change in FIQR between baseline and post-treatment at 12 weeks. Analysis of covariance (ANCOVA) will be used to assess significance of changes in FIQR at 12 weeks, adjusting for baseline FIQR as a covariate, as outlined in equation (1) below.

$$FIQR_{posttreatment} = a + b * FIQR_{baseline} + c * group \quad (1)$$

Using the change in FIQR score as the outcome measure is susceptible to regression to the mean, and does not take into account baseline imbalance in FIQR[96; 97], which is possible in a relatively small trial[135]. Thus, ANCOVA adjusting for the baseline score is the most appropriate analysis method in this context. In addition, the estimated mean change from baseline to 12 weeks and associated standard error and 95%CI will be reported.

D.9.2.2 Secondary Outcomes

FIQR over time: Changes in FIQR over time will be assessed using linear mixed models. FIQR at 3, 6 and 12 months will be the dependent variable, with FIQR at baseline included as a time-invariant covariable. Study participants will be considered as random effects, and the treatment group (Sleepio vs control) and assessment time point as fixed effects, as outline below in equation (2).

$$FIQR_{posttreatment} = a + b * FIQR_{baseline} + c * group + d * timepoint + (1|subject) \quad (2)$$

In addition, a model fitting a group*time interaction will be examined to look at the differential trajectories in FIQR over time between groups, as shown in equation (3) below.

$$FIQR_{posttreatment} = a + b * FIQR_{baseline} + c * group * timepoint + (1|subject) \quad (3)$$

As above, the estimated mean change in FIQR from baseline to each time point with corresponding SE and 95%CI will be reported.

Cognitive Function: Changes in subjective cognitive complaints assessed via the British Columbia Cognitive Complaints Inventory (BC-CCI) at 3, 6, and 12 months, will be assessed using the same methods outlined above for FIQR, and the mean change with associated SE and 95%CI will be presented.

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Changes in NVT task performance will be measured using sensitivity (d') as the outcome variable, analysed using the same methods outlined above, and the mean change with associated SE and 95%CI will be presented.

Sleep Quality: Changes in the Insomnia Severity Index (ISI) at 3, 6, and 12 months. The ISI was selected as the self-report measure of sleep quality, as it is more likely to display measurement invariance (i.e. measure the same construct over time) compared to the PSQI[81]. Sleep efficiency, total sleep time, and wake after sleep onset (WASO) assessed via actigraphy at 3 months. As above, all analyses will be carried out as described above, using ANCOVA and LMMs, and the mean change with associated SE and 95%CI will be presented.

Pain: Changes in the Short Form 36 Bodily Pain Scale (SF-36 BPS) at 3, 6, and 12 months. As above, all analyses will be carried out as described above, using ANCOVA and LMMs, and the mean change with associated SE and 95%CI will be presented.

There will be no adjustment for multiple comparisons of non-imaging outcomes. In the setting of clinical trials, multiplicity adjustment is often inappropriate as it assumes all tested hypotheses are independent and equally relevant, which is rarely the case in this setting (for example, sleep quality, sleep efficiency, subjective dyscognition, and objective sustained attention are likely to be interrelated). Instead, adjustments like the Bonferroni correction can overcorrect, reducing statistical power and potentially

obscuring meaningful clinical findings, especially when endpoints are interrelated and when clinical interpretation is more relevant than strict statistical significance[403].

Neuroimaging Outcomes:

Magnetic Resonance Spectroscopy (MRS): Changes in neurotransmitter concentrations in the posterior insula at 12 weeks.

Resting-State Functional MRI (fMRI): Changes in neuromarkers of sustained attention at 12 weeks. Detailed neuroimaging analyses are described in the subsequent chapter.

Covariate adjustment: Baseline values of the outcome measures will be included as a covariate for adjustment. Change scores will not be analysed.

Sensitivity analyses: As a sensitivity analysis, age at baseline will be included as a covariate given its known strong association with cognition. It will be modelled as a non-linear term given its non-linear association with cognitive abilities.

Missing Data Handling:

Primary Method - Multiple Imputation (MI): If missing data exceeds 5% and does not exceed 40% for an outcome measure, missing data will be imputed using a multiple imputation approach under the assumption of Missing At Random (MAR)[74; 216]. Below 5%, the impact of missing data is likely to be negligible, while above 40% missing, interpretation of the results is likely to be compromised and imputation is unlikely to resolve this[490]. The imputation model will include all baseline covariates,

outcome variables, and other auxiliary variables predictive of missingness to improve the robustness of the imputations. A minimum of 20 imputations will be generated, as determined by the rule of thumb that the number of imputations equals the percentage of missing data[490]. These datasets will be analysed individually, and results will be combined using Rubin's rules to account for the variability between imputations.

Sensitivity Analysis: Sensitivity to the MAR assumption will be assessed using pattern-mixture models or other appropriate methods to test robustness under Missing Not At Random (MNAR) assumptions.

Reporting: The extent of missing data, reasons for missingness (if available), and characteristics of participants with missing data compared to those with complete data will be reported. Results of the imputed analyses will be compared with complete case analyses to highlight any differences in conclusions.

Other: Number and type of adverse events will be reported.

E Appendix E: Chapter 6

E.1 Brain Imaging

Fibromyalgia participants in the trial arm were invited to undergo a brain MRI during the baseline assessment. This included a 12-minute resting state functional MRI scan. These images underwent the following pre-processing steps.

E.1.1 Data organisation

The organisation and preparation of MRI data for analysis involved several key steps. First, participant folders were checked to ensure the required imaging files (T1, fieldmap, and rs-fMRI) were present, and any missing files were recorded. Next, the relevant images were copied into a designated directory for each participant, labelled with their study ID number (in the format 'FM_OX_PAIN_1234'), and missing images were checked again to ensure completeness. Metadata reports were then generated for each image file using `fslinfo`, summarising key image information, and stored within each participant's folder. The images were named consistently for easier identification, such as labelling the resting-state fMRI as resting.nii.gz and the T1-weighted images as structural.nii.gz.

E.1.2 Pre-processing

Prior to analysis, a series of pre-processing steps were applied using tools from FMRIB's Software Library (FSL)[219].

E.1.3 Brain Extraction

Non-brain structures were removed from MRI images using the Brain Extraction Tool (BET), with a threshold of 0.5 initially set. All images were checked manually for successful brain extraction, and it was re-run with a different threshold if required.

E.1.4 Registration

Images were aligned (registered) to permit comparisons both within and between participants. Functional images were aligned to structural T1 images using FLIRT (FMRIB's Linear Image Registration Tool [218]), using boundary-based registration (BBR) [181]. Images were then registered to standard MNI-152 space using FNIRT (FMRIB's Nonlinear Image Registration Tool [13]) to enable comparison across participants.

E.1.5 B0 Unwarping

Magnetic field inhomogeneities (B0 field) can lead to signal loss and image distortion, particularly in the frontal and temporal lobes due to the presence of the head within the scanner and air-filled sinuses. To minimise these inhomogeneities during scanning, shimming a process of adjusting the scanner's coils, was employed. However, complete elimination of these inhomogeneities would also negate the BOLD effect, which relies on local field disruptions caused by deoxyhaemoglobin. Therefore, signal loss around specific areas remains a challenge, and distortions were corrected using a fieldmap during image analysis.

Fieldmaps were obtained for all sessions and applied during analysis using the MELODIC tool in FSL[219]. Magnitude and phase images were acquired, and careful brain extraction using BET was performed on the magnitude images to ensure accurate

fieldmap generation. A key requirement was that brain extraction be very tight, excluding non-brain voxels and those with partial volume contributions, as these regions tend to be noisy in the phase images. If BET removed too much brain tissue, manual correction was performed by aligning the magnitude image with the structural image and applying a brain mask derived from the structural scan. Brain extraction was further refined by eroding the extracted brain to remove noisy voxels from the edge of the brain, which can affect subsequent processing steps. The phase difference image was reviewed before deciding whether to erode, ensuring that only relevant brain areas were retained for accurate fieldmap generation. A tight mask, even if it excluded some brain voxels, was acceptable as the fieldmap extrapolates beyond the mask.
Fieldmap preparation was conducted using the FSL tool `fsl_prepare_fieldmap` with the SIEMENS acquisition settings and the calculated difference in echo times (diffTE=2.46ms). The resulting fieldmap was applied to the BOLD data to correct for distortions during preprocessing.

E.1.6 Noise Correction

To minimise motion artefacts, participants were instructed to remain as still as possible during the scan, and padding was provided around pressure points, particularly the head, to enhance comfort and reduce movement. Despite these precautions, motion and physiological noise are inevitable during MRI acquisition. To address these issues, several preprocessing steps were employed.
Motion artefacts were first corrected using the McFlirt tool[218], which regressed out motion parameters collected during the scan. However, McFlirt cannot correct for physiological noise arising from sources such as cardiac or respiratory cycles. To

address these, Independent Component Analysis (ICA) was applied to separate and remove noise components from the data.

ICA splits the data into temporal and spatial components, generating a spatial map and time course for each component. These components were then classified as either signal or noise based on their spatial and temporal characteristics. As no suitable pre-existing training datasets were available for the fibromyalgia population in this study, I manually created a new training set. Hand-classification of components was performed on a subset of 12 participants, sampled across the data collection period, using guidelines developed by Griffanti et al.[182]. After manual classification, the resulting training set was applied to the FIX automated denoising tool, which was used to classify the remaining dataset and remove noise components[183; 394].

For automated processing, the MELODIC GUI was used, performing ICA with specific preprocessing parameters. ICA was run on all participants using a batch script, and outputs were stored in a session-specific ICA directory. The training weights generated from hand-labelled components were applied to the FIX algorithm to remove noise components. The final cleaned data (filtered_func_data_clean.nii.gz) for each participant was visually inspected using *Fsleyes* to confirm successful denoising by comparing the pre-processed and cleaned datasets. After denoising, the cleaned data was registered to standard space using a warp transformation, applied via a batch script for efficiency across participants.

E.1.7 Slice Timing Correction

To address timing differences in slice acquisition, slice timing correction was applied using FEAT (FMRIB's Expert Analysis Tool) [505]. This correction adjusts the timeseries

of each slice to align them temporally, ensuring that data from different slices is synchronised and accurately reflects the modelled hemodynamic response. This step ensures valid temporal comparisons across the entire dataset.

E.1.8 Spatial Smoothing

To reduce spatial noise and improve the signal-to-noise ratio, spatial smoothing was applied to the data. A Gaussian smoothing kernel with a full width at half maximum (FWHM) of 5mm was used. This smoothing process reduces the effects of high-frequency spatial noise by averaging nearby voxels, improving the overall quality of the functional images and helping to ensure more robust statistical analysis by enhancing regional activation signals.

E.1.9 Temporal Filtering

Temporal filtering was applied to remove noise frequencies that were not relevant to the signal of interest. Low-pass filtering was implemented to eliminate high-frequency noise from the data, while high-pass filtering was used to remove low-frequency drift, such as scanner artefacts or physiological fluctuations. These filters were applied using FEAT[505], with cut-off values tailored to retain frequencies associated with the hemodynamic response of interest, ensuring that the key signals were preserved and artefactual noise was minimised.

E.1.10 Imaging-derived Phenotype

Building on work described in chapter 4 (Section 4.3.5), suggesting that PAG-Amygdala connectivity may play a key role in sleep and cognitive problems in chronic pain, this

measure was extracted as an imaging-derived phenotype (IDP) of interest in this study. The methods were similar to those described in chapter 4 (Section). Briefly, the rs-fMRI functional 4-D time series were extracted from the pre-processed rs-fMRI images registered to MNI152 space for each subject, using region-of-interest masks for the PAG and Amygdala with fslmeants from FSL. The correlation between the time series for these ROIs was calculated (as only two ROIs were examined, the partial and full correlation are equivalent), and this was standardised using Fisher's r-to-Z transformation.

E.2 Baseline characteristics for included compared to excluded fibromyalgia participants

	Total	Excluded (no NVT)	Included (NVT)	P-value
	(N=107)	(N=35)	(N=72)	
Age (years)				
Mean (SD)	47.1 (14.3)	46.5 (13.9)	47.3 (14.6)	0.968
Missing	1 (0.9%)	1 (2.9%)	0 (0%)	
Sex				
Female	99 (93 %)	33 (94 %)	66 (92 %)	0.906
Male	6 (6 %)	1 (3 %)	5 (7 %)	
Prefer not to say	1 (1 %)	0 (0 %)	1 (1 %)	
Missing	1 (0.9%)	1 (2.9%)	0 (0%)	
White ethnicity				
Mean (SD)	0.896 (0.306)	0.882 (0.327)	0.903 (0.298)	0.95
Missing	1 (0.9%)	1 (2.9%)	0 (0%)	
University Degree				
Mean (SD)	0.364 (0.484)	0.257 (0.443)	0.417 (0.496)	0.277
Employment Status				
Carer	1 (1 %)	1 (3 %)	0 (0 %)	0.905
Full time education	1 (1 %)	0 (0 %)	1 (1 %)	
Full time employment	32 (30 %)	6 (17 %)	26 (36 %)	
Part time employment	25 (23 %)	10 (29 %)	15 (21 %)	
Prefer not to answer	3 (3 %)	0 (0 %)	3 (4 %)	
Retired	13 (12 %)	5 (14 %)	8 (11 %)	
Unable to work due to illness	28 (26 %)	11 (31 %)	17 (24 %)	
Unemployed	3 (3 %)	1 (3 %)	2 (3 %)	
Missing	1 (0.9%)	1 (2.9%)	0 (0%)	
Symptom duration (years)				
Mean (SD)	10.9 (10.0)	10.3 (9.11)	11.2 (10.5)	0.914
Missing	2 (1.9%)	2 (5.7%)	0 (0%)	
Opioids				
No Opioids	45 (42 %)	1 (3 %)	44 (61 %)	0.759
Opioids	30 (28 %)	2 (6 %)	28 (39 %)	
Missing	32 (29.9%)	32 (91.4%)	0 (0%)	
TCAs				
No TCAs	58 (54 %)	3 (9 %)	55 (76 %)	0.746
TCAs	17 (16 %)	0 (0 %)	17 (24 %)	
Missing	32 (29.9%)	32 (91.4%)	0 (0%)	
Gabapentin/Pregabalin				

	Total	Excluded (no NVT)	Included (NVT)	P-value
No Gaba	64 (60 %)	1 (3 %)	63 (88 %)	0.0565
Gaba	11 (10 %)	2 (6 %)	9 (12 %)	
Missing	32 (29.9%)	32 (91.4%)	0 (0%)	
Number of Analgesics				
0	67 (63 %)	32 (91 %)	35 (49 %)	<0.001
1	22 (21 %)	2 (6 %)	20 (28 %)	
2	18 (17 %)	1 (3 %)	17 (24 %)	
Fibromyalgianess (0-31)				
Mean (SD)	19.1 (5.85)	18.3 (7.08)	19.5 (5.16)	0.624
Widespread Pain Index (0-19)				
Mean (SD)	11.1 (4.72)	10.9 (5.05)	11.3 (4.59)	0.938
Symptom Severity Score (0-12)				
Mean (SD)	7.95 (2.23)	7.40 (2.64)	8.22 (1.96)	0.199
Fibromyalgia Impact Questionnaire Revised (0-100)				
Mean (SD)	58.5 (18.3)	64.7 (19.2)	55.6 (17.3)	0.0671
Missing	5 (4.7%)	3 (8.6%)	2 (2.8%)	
PainDETECT (0-38)				
Mean (SD)	19.1 (6.59)	20.5 (5.92)	18.4 (6.82)	0.343
Missing	5 (4.7%)	3 (8.6%)	2 (2.8%)	
British Columbia Cognitive Complaints Inventory				
Mean (SD)	11.4 (3.86)	11.7 (4.51)	11.3 (3.56)	0.9
Missing	4 (3.7%)	3 (8.6%)	1 (1.4%)	
Patient Health Questionnaire 9				
Mean (SD)	12.8 (6.02)	14.1 (6.93)	12.2 (5.47)	0.297
Generalised Anxiety Disorder Assessment 7				
Mean (SD)	7.66 (5.74)	9.57 (6.13)	6.74 (5.34)	0.055
Insomnia Severity Index				
Mean (SD)	16.6 (6.47)	16.1 (7.83)	16.8 (5.74)	0.84
Total Sleep Time (hours)				
Mean (SD)	5.64 (1.47)	5.38 (1.61)	5.75 (1.41)	0.526
Missing	10 (9.3%)	6 (17.1%)	4 (5.6%)	
Time in bed (hours)				
Mean (SD)	8.75 (2.37)	8.81 (3.59)	8.73 (1.56)	0.987
Missing	5 (4.7%)	3 (8.6%)	2 (2.8%)	
Sleep efficiency, %				
Mean (SD)	64.7 (16.6)	60.4 (17.6)	66.6 (15.9)	0.25
Missing	10 (9.3%)	6 (17.1%)	4 (5.6%)	

Supplementary Table E-1. Baseline characteristics of participants included in the analysis compared to those excluded.

Fibromyalgia symptom severity was assessed using the Fibromyalgia Impact Questionnaire Revised (FIQR), with higher scores indicating more severe symptoms. The Fibromyalgia Index (FMI) is the sum of the Widespread Pain

Index (WPI) and Symptom Severity Scale (SSS). Depression was measured using the Patient Health Questionnaire 9-item (PHQ-9), with higher scores indicating more severe depression symptoms. Anxiety was assessed using the Generalised Anxiety Disorder 7-item scale (GAD-7), with higher scores indicating more severe anxiety symptoms. Brain-fog was measured using the British Columbia Cognitive Complaints Inventory (BC-CCI), where higher scores reflect greater cognitive difficulties. Neuropathic pain symptoms were assessed using PainDETECT, with higher scores indicating more severe neuropathic symptoms. Insomnia was evaluated using the Insomnia Severity Index (ISI), with higher scores representing greater severity. Total sleep time, time in bed, and sleep efficiency were self-reported and taken from the Pittsburgh Sleep Quality Inventory (PSQI). Note that analgesia use was asked during the in-person study visit, while the other measures were collected online. SD = standard deviation.

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	Total	Excluded (No MRI)	Included (MRI)	P-value
	(N=72)	(N=17)	(N=55)	
Age (years)				
Mean (SD)	47.3 (14.6)	46.4 (13.5)	47.6 (15.0)	0.955
Sex				
Female	66 (92 %)	14 (82 %)	52 (95 %)	0.389
Male	5 (7 %)	2 (12 %)	3 (5 %)	
Prefer not to say	1 (1 %)	1 (6 %)	0 (0 %)	
White ethnicity				
Mean (SD)	0.903 (0.298)	0.882 (0.332)	0.909 (0.290)	0.95
University Degree				
Mean (SD)	0.417 (0.496)	0.529 (0.514)	0.382 (0.490)	0.564
Employment Status				
Full time employment	26 (36 %)	5 (29 %)	21 (38 %)	NA
Part time employment	15 (21 %)	4 (24 %)	11 (20 %)	
Full time education	1 (1 %)	1 (6 %)	0 (0 %)	
Retired	8 (11 %)	2 (12 %)	6 (11 %)	
Carer	0 (0 %)	0 (0 %)	0 (0 %)	
Unable to work due to illness	17 (24 %)	2 (12 %)	15 (27 %)	
Unemployed	2 (3 %)	2 (12 %)	0 (0 %)	
Prefer not to answer	3 (4 %)	1 (6 %)	2 (4 %)	
Symptom duration (years)				
Mean (SD)	11.2 (10.5)	9.65 (7.58)	11.7 (11.2)	0.784
Opioids				
No Opioids	44 (61 %)	13 (76 %)	31 (56 %)	0.313
Opioids	28 (39 %)	4 (24 %)	24 (44 %)	
TCAs				
No TCAs	55 (76 %)	15 (88 %)	40 (73 %)	0.396
TCAs	17 (24 %)	2 (12 %)	15 (27 %)	
Gabapentin/Pregabalin				
No Gabapentinoids	63 (88 %)	14 (82 %)	49 (89 %)	0.819
Gabapentinoids	9 (12 %)	3 (18 %)	6 (11 %)	
Number of Analgesics				
0	35 (49 %)	10 (59 %)	25 (45 %)	0.782
1	20 (28 %)	5 (29 %)	15 (27 %)	
2	17 (24 %)	2 (12 %)	15 (27 %)	
Fibromyalgianess (0-31)				
Mean (SD)	19.5 (5.16)	19.5 (6.20)	19.5 (4.86)	0.999
Widespread Pain Index (0-19)				
Mean (SD)	11.3 (4.59)	11.2 (4.89)	11.3 (4.54)	1
Symptom Severity Score (0-12)				

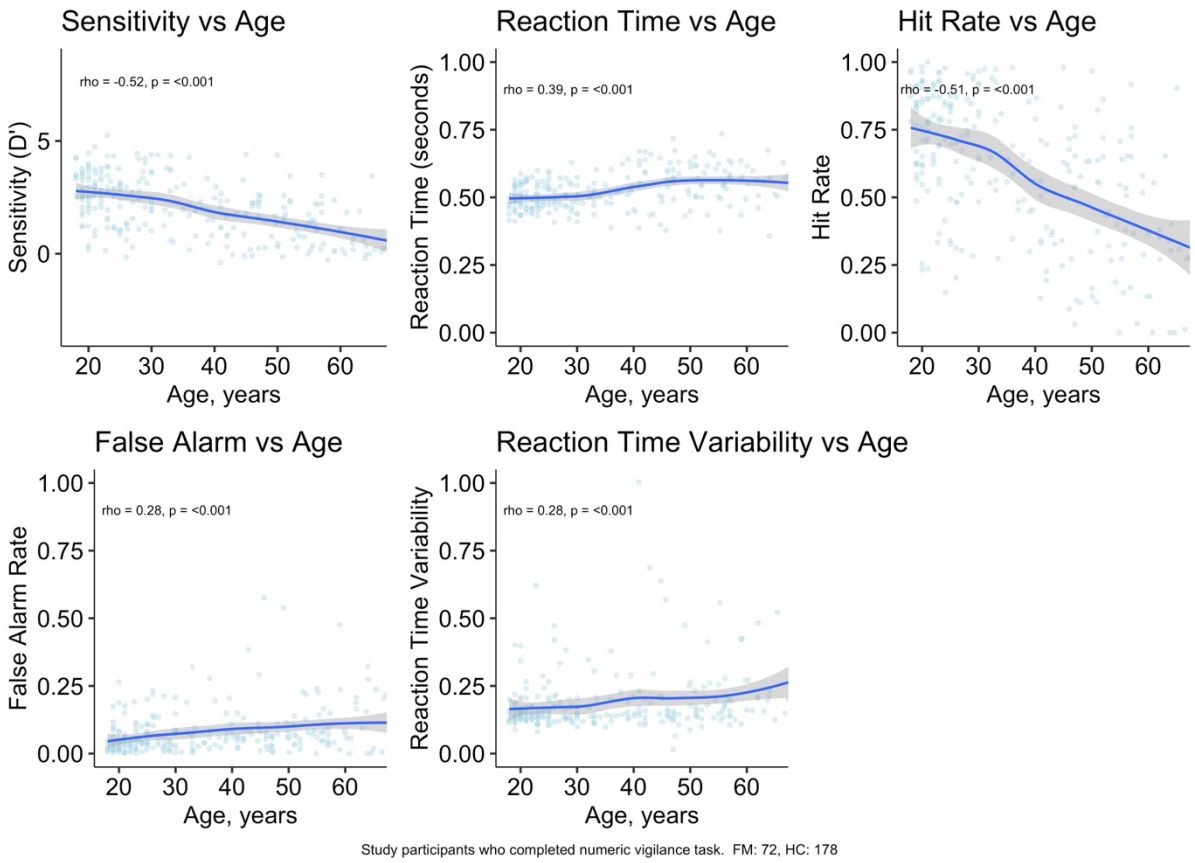
	Total	Excluded (No MRI)	Included (MRI)	P-value
Mean (SD)	8.22 (1.96)	8.29 (2.85)	8.20 (1.63)	0.985
Fibromyalgia Impact Questionnaire Revised (0-100)				
Mean (SD)	55.6 (17.3)	51.9 (17.2)	56.7 (17.4)	0.625
Missing	2 (2.8%)	1 (5.9%)	1 (1.8%)	
PainDETECT (0-38)				
Mean (SD)	18.4 (6.82)	16.6 (6.66)	19.0 (6.82)	0.455
Missing	2 (2.8%)	1 (5.9%)	1 (1.8%)	
British Columbia Cognitive Complaints Inventory				
Mean (SD)	11.3 (3.56)	11.7 (3.53)	11.2 (3.59)	0.891
Missing	1 (1.4%)	1 (5.9%)	0 (0%)	
Patient Health Questionnaire 9				
Mean (SD)	12.2 (5.47)	11.5 (6.52)	12.4 (5.16)	0.83
Generalised Anxiety Disorder Assessment 7				
Mean (SD)	6.74 (5.34)	6.06 (4.26)	6.95 (5.65)	0.837
Insomnia Severity Index				
Mean (SD)	16.8 (5.74)	15.2 (7.12)	17.4 (5.22)	0.39
Total Sleep Time (hours)				
Mean (SD)	5.75 (1.41)	5.75 (1.24)	5.75 (1.47)	1
Missing	4 (5.6%)	1 (5.9%)	3 (5.5%)	
Time in bed (hours)				
Mean (SD)	8.73 (1.56)	8.39 (1.34)	8.83 (1.62)	0.614
Missing	2 (2.8%)	1 (5.9%)	1 (1.8%)	
Sleep efficiency, %				
Mean (SD)	66.6 (15.9)	70.0 (16.9)	65.5 (15.6)	0.619
Missing	4 (5.6%)	1 (5.9%)	3 (5.5%)	

Supplementary Table E-2. Baseline characteristics of participants included in the RSFC analysis compared to those excluded (i.e. no MRI).

Fibromyalgia symptom severity was assessed using the Fibromyalgia Impact Questionnaire Revised (FIQR), with higher scores indicating more severe symptoms. The Fibromyalgia Index (FMI) is the sum of the Widespread Pain Index (WPI) and Symptom Severity Scale (SSS). Depression was measured using the Patient Health Questionnaire 9-item (PHQ-9), with higher scores indicating more severe depression symptoms. Anxiety was assessed using the Generalised Anxiety Disorder 7-item scale (GAD-7), with higher scores indicating more severe anxiety symptoms. Brain-fog was measured using the British Columbia Cognitive Complaints Inventory (BC-CCI), where higher scores reflect greater cognitive difficulties. Neuropathic pain symptoms were assessed using PainDETECT, with higher scores indicating more severe neuropathic symptoms. Insomnia was evaluated using the Insomnia Severity Index (ISI), with higher scores representing greater severity. Total sleep time, time in bed, and sleep efficiency were self-reported and taken from the Pittsburgh Sleep Quality Inventory (PSQI). Note that brain MRI was only offered to participants who attended the in-person study visit, while the other measures were collected online. SD = standard deviation.

E.3 Relationship between sustained attention with age

Given the known important relationship between age and cognitive performance, the relationship between age and performance on the NVT was examined. A comparison of polynomial models for all variables found that the linear model fit best, apart from reaction time for which a cubic model fit best.



Supplementary Figure E-1. Relationship between age and performance on number vigilance task.

All metrics, apart from reaction time, displayed a broadly linear association with age, with the strongest association observed for hit rate and age. Reaction time displayed a quadratic association with age. Rho, spearman correlation coefficient.

E.4 Objective 1: Compare sustained attention performance between fibromyalgia patients and healthy controls

E.4.1 Objective 1: Group differences in sustained attention

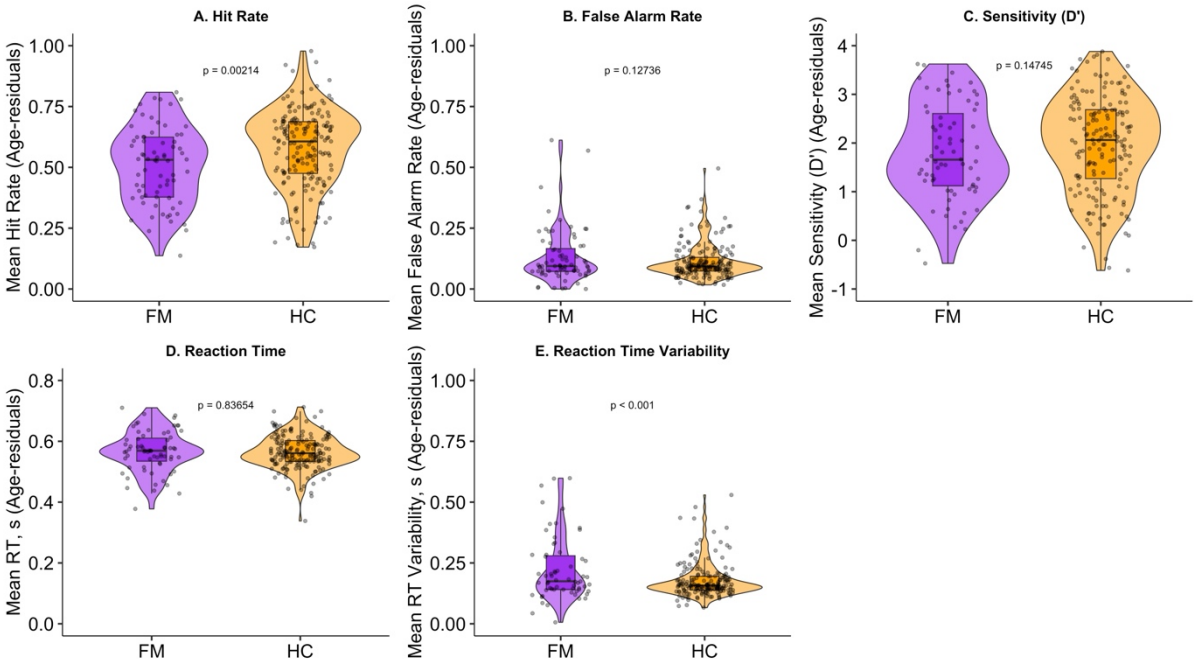
The fibromyalgia group had worse performance across all domains of sustained attention on the NVT, apart from reaction time (Supplementary Table E-3 **&** Supplementary Figure E-2). While healthy controls correctly identified two-thirds of correct digits (hit rate 0.666), the fibromyalgia group identified just over two-fifths (hit rate 0.431, Supplementary Figure E-2**A,** P=0.009). The fibromyalgia group also displayed a higher false alarm rate (0.108 vs 0.069, P=0.004), however this difference was reduced in age-adjusted values (0.131 vs 0.113, Supplementary Figure E-2**B,** P=0.312). Of note, there was no difference in reaction time for correct responses (0.537 vs 0.52 seconds, P=0.226), however the fibromyalgia group did display a significantly higher reaction time variability (0.251 vs 0.166, P=0.001). These group differences were attenuated after age-adjustment, but remained present for hit rate and reaction time variability. On average, the fibromyalgia group also reported lower levels of motivation (0.326 vs 0.481, P<0.001) and higher levels of fatigue (0.729 vs 0.638, P=0.03) compared to healthy controls.

	Total	FM	HC	P
	(N=250)	(N=72)	(N=178)	
Hit Rate				
Mean (SD)	0.599 (0.263)	0.431 (0.264)	0.666 (0.231)	<0.001
Age-adjusted Hit Rate				
Mean (SD)	0.556 (0.163)	0.507 (0.157)	0.576 (0.161)	0.00921
False Alarm Rate				
Mean (SD)	0.0798 (0.0858)	0.108 (0.112)	0.0685 (0.0701)	0.00448
Age-adjusted False Alarm Rate				
Mean (SD)	0.118 (0.0854)	0.131 (0.113)	0.113 (0.0713)	0.312
Sensitivity (D')				
Mean (SD)	2.04 (1.30)	1.40 (1.36)	2.30 (1.18)	<0.001
Age-adjusted Sensitivity (D')				
Mean (SD)	2.04 (1.10)	1.88 (1.05)	2.10 (1.12)	0.35
Reaction time, sec				
Mean (SD)	0.524 (0.0680)	0.537 (0.0777)	0.520 (0.0635)	0.226
Missing	6 (2.4%)	5 (6.9%)	1 (0.6%)	
Age-adjusted Reaction Time, sec				
Mean (SD)	0.565 (0.0592)	0.566 (0.0681)	0.565 (0.0557)	0.979
Missing	6 (2.4%)	5 (6.9%)	1 (0.6%)	
Reaction time variability				
Mean (SD)	0.189 (0.115)	0.251 (0.173)	0.166 (0.0723)	<0.001
Missing	6 (2.4%)	6 (8.3%)	0 (0%)	
Age-adjusted Reaction Time Variability				
Mean (SD)	0.194 (0.108)	0.235 (0.167)	0.178 (0.0716)	0.0014
Missing	11 (4.4%)	8 (11.1%)	3 (1.7%)	
Pain, VAS				
Mean (SD)	0.528 (0.251)	0.528 (0.251)		
Missing	178 (71.2%)	0 (0%)	178 (100%)	
Motivation, VAS				
Mean (SD)	0.436 (0.260)	0.326 (0.227)	0.481 (0.260)	<0.001
Fatigue, VAS				
Mean (SD)	0.664 (0.246)	0.729 (0.203)	0.638 (0.257)	0.0301
Missing	1 (0.4%)	1 (1.4%)	0 (0%)	

Supplementary Table E-3. Performance on number vigilance task for participants with fibromyalgia compared to healthy controls.

Mean (SD) performance across all blocks reported. Comparisons between groups were conducted using two-sample t-tests. Hit rate is the proportion of correctly identified target digits (hits) relative to all target digits. False alarm rate is the proportion of non-target digits incorrectly identified as targets. Sensitivity (d') was derived by subtracting the z-score of the false alarm rate from the z-score of the hit rate, with higher values indicating greater sensitivity. Reaction time is the time taken to respond for correct digits only (in seconds). Reaction time variability was derived by dividing the standard deviation of correct reaction times by the mean reaction time. Pain, motivation, and fatigue were assessed using a visual analogue scale (VAS), and reported on a scale of 0 to 1. Healthy controls were not asked

about pain as this parameter was introduced later in the task. Both unadjusted and age-adjusted performance metrics presented. FM, fibromyalgia. HC, healthy controls.

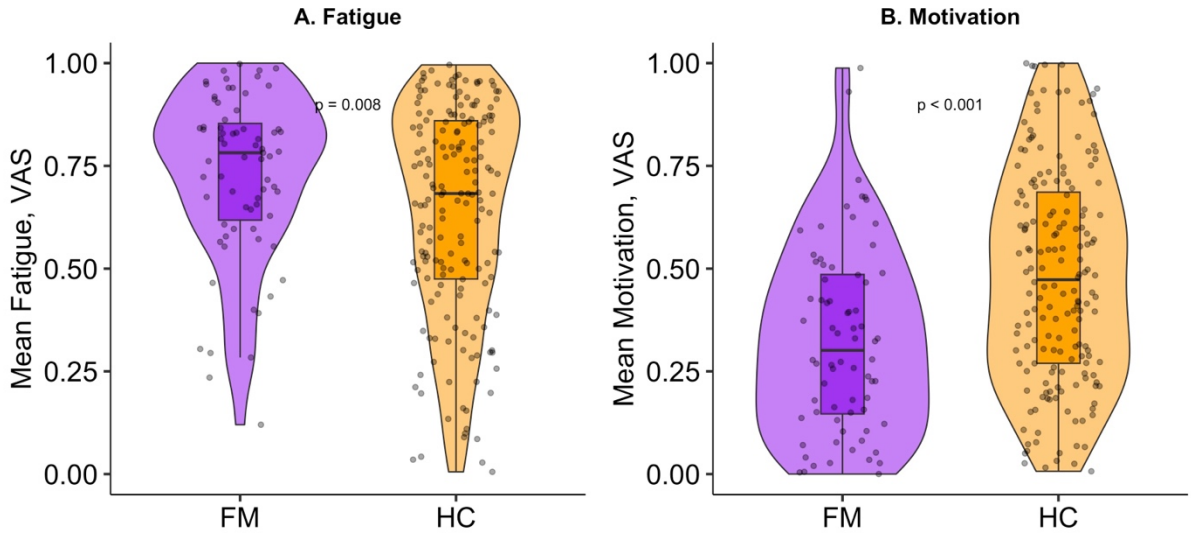


Supplementary Figure E-2. Fibromyalgia patients (FM) were worse at detecting targets and had more variable response times in the number vigilance task (NVT).

Patients with fibromyalgia (FM) displayed a lower hit rate (A) and increased reaction time variability (E) compared to healthy controls (HCs). There was no difference in false alarm rate (incorrect responses) (B), sensitivity (d') (C) or reaction time (D). Each panel displays violin plots overlaid with box-and-whisker plots to illustrate the distribution of responses within each group. The central line represents the mean, with whiskers indicating ±1 standard deviation (SD). P-values are derived from two-sample t-tests comparing fibromyalgia and HC groups for each NVT performance metric. FM, fibromyalgia. HC, healthy controls.

E.5 Objective 1: Group differences in fatigue and motivation

Patients with fibromyalgia reported higher mean levels of fatigue (Supplementary Figure E-3**A**, 0.729 vs 0.638; P=0.008) and lower motivation (Supplementary Figure E-3**B**, 0.326 vs 0.481; P<0.001) compared to healthy controls during the NVT. The fibromyalgia group also displayed a narrower spread of values, with more fibromyalgia patients reporting both high and low values of fatigue and motivation, respectively.



Supplementary Figure E-3. Fibromyalgia patients (FM) reported worse fatigue and lower motivation during the number vigilance task (NVT).

Patients with fibromyalgia (FM) reported greater levels of fatigue (A) and lower levels of motivation (B) compared to healthy controls (HCs)). Each panel displays violin plots overlaid with box-and-whisker plots to illustrate the distribution of responses within each group. The central line represents the mean, with whiskers indicating ±1 standard deviation (SD). P-values are derived from independent t-tests comparing fibromyalgia and HC groups for each NVT behavioural metric. FM, fibromyalgia. HC, healthy controls. VAS, visual analogue scale.

E.6 Objective 2

E.6.1 Objective 2: Effect of pain, fatigue, and motivation on sustained attention

Participants with higher levels of self-reported pain, fatigue and lower motivation were all associated with worse focus (greater RT variability) and more errors (lower D') on the NVT task (Supplementary Figure E-4). Higher pain levels were significantly associated with greater reaction time variability (Supplementary Figure E-4**B,** P=0.0056), and lower sensitivity (Supplementary Figure E-4**C**, P<0.001). There was no significant association between pain intensity or reaction time (Supplementary Figure E-4**A**, P=0.27).

Baseline pain explained a substantial proportion of the variance in performance metrics, contributing to a change in R^2 of 10.9% for reaction time variability, and 8.8% for sensitivity.

Higher levels of fatigue were similarly significantly associated with greater reaction time variability (Supplementary Figure E-4**E,** P<0.001), and lower sensitivity (Supplementary Figure E-4**F**, P=0.003). There was also no significant association between pain intensity or reaction time (Supplementary Figure E-4**D**, P=0.28).

Baseline fatigue explained a larger proportion of the variance in performance metrics compared to pain, contributing to a change in R^2 of 16.1% for reaction time variability, and 7.0% for sensitivity.

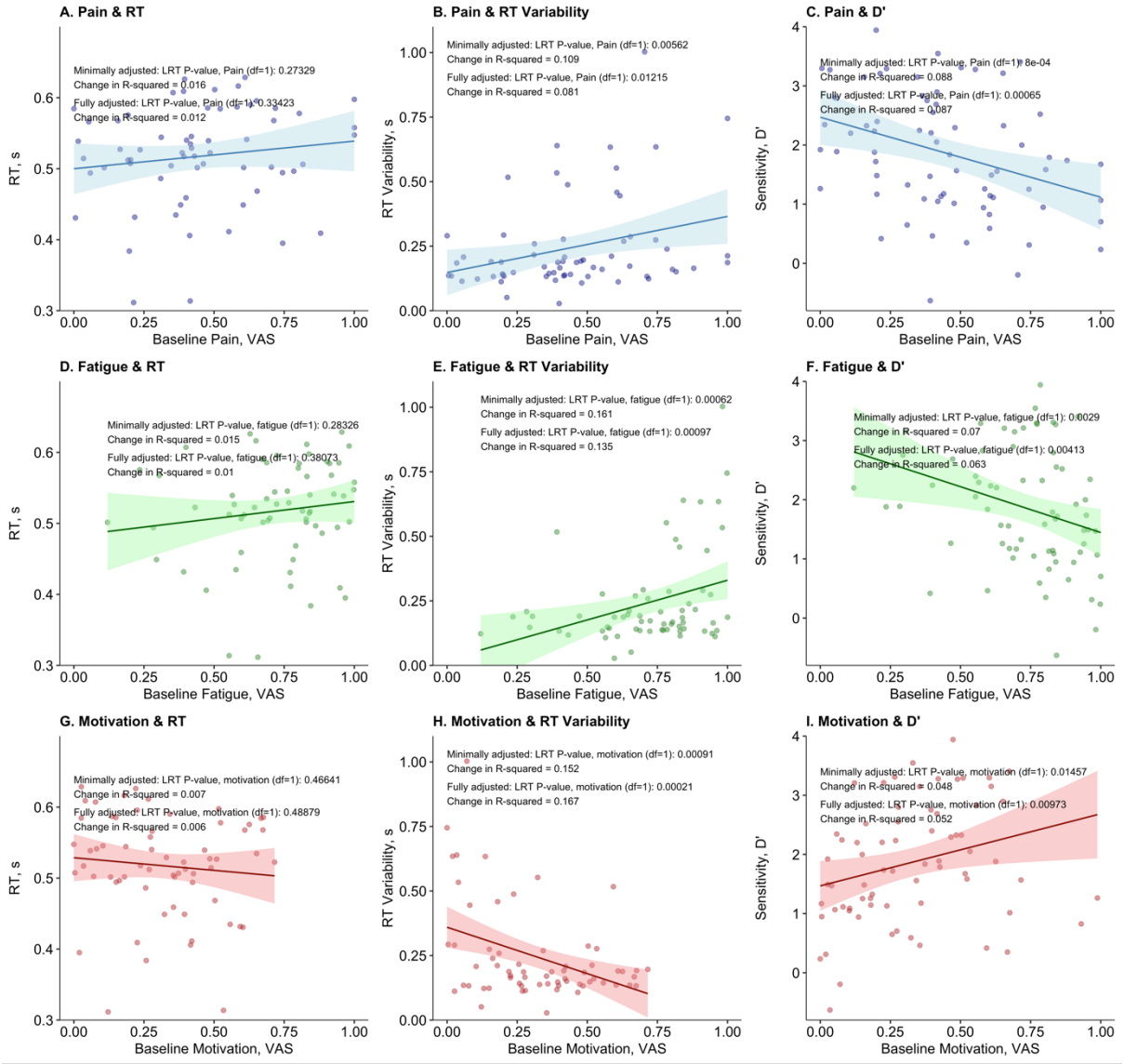
Finally, lower motivation levels were associated with greater reaction time variability (Supplementary Figure E-4**H,** P<0.001), and lower sensitivity (Supplementary Figure E-4**I**, P=0.015). As with pain and fatigue, there was also no significant association between pain intensity or reaction time (Supplementary Figure E-4**D**, P=0.47).

Appendix E

Motivation explained a similar proportion of the variance in performance metrics as fatigue, contributing to a change in R^2 of 15.2% for reaction time variability, and 4.8% for sensitivity.

Adjusting for socio-demographic confounders (education and employment status), and analgesia use (opioids, tricyclic antidepressants, and gabapentinoids) did not attenuate these relationships.

These results suggest that levels of pain and fatigue, and lower levels of motivation, negatively impact attentional focus (as indicated by reaction time variability) and task accuracy (sensitivity) in fibromyalgia.

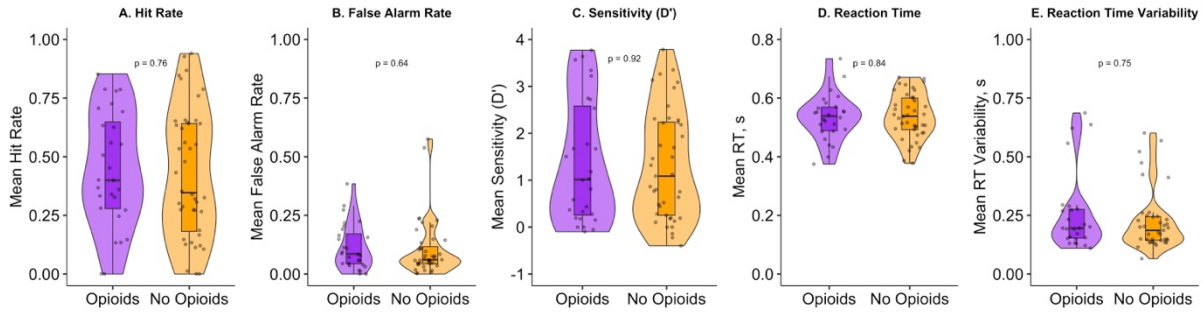


Supplementary Figure E-4. Relationship between baseline pain, fatigue, and motivation levels and task performance in fibromyalgia.

Relationships between levels of pain (A-C), fatigue (D-F), and motivation (G-I) at baseline and subsequent NVT performance metrics are displayed for fibromyalgia patients. Higher levels of baseline pain, fatigue, and lower motivation all associated with worse focus (greater RT variability) and more errors (worse sensitivity). There was no significant relationship with reaction time. All measures recorded on a VAS, with higher values indicating worse pain and fatigue, and more motivation. Minimally adjusted model includes age and sex. Fully adjusted model includes education (degree, no degree), employment status (employed, not employed), and analgesia use (opioids, tricyclic antidepressants, or gabapentinoids). Training blocks omitted. Regression slopes with 95% confidence intervals are shown. Likelihood ratio test (LRT) p-values and changes in R^2 are provided for the contribution of FIQR in the models. VAS, visual analogue scale; s, second; FM, fibromyalgia; LRT, likelihood ratio test; df, degrees of freedom.

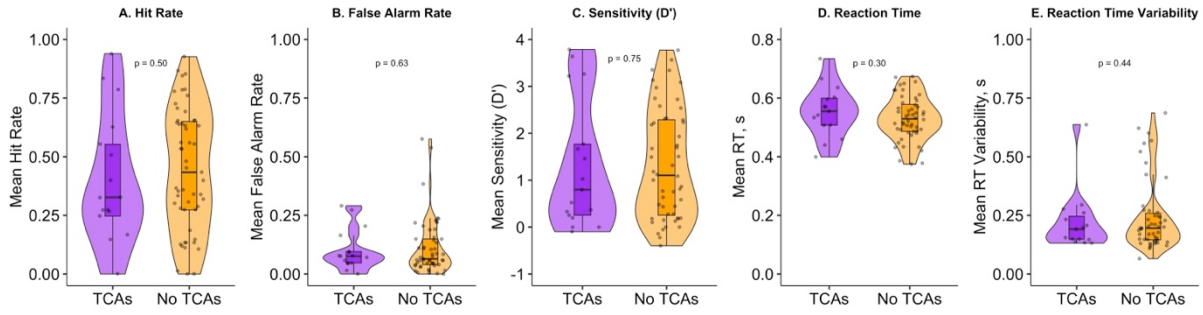
E.6.2 Objective 2: Analgesia Use & Sustained Attention

The type or number of current analgesia medications had no impact on sustained attention in fibromyalgia. There was no association between current opioid use (Supplementary Figure E-5**A-E,** P>0.05 for all), tricyclic antidepressant use (Supplementary Figure E-6**A-E,** P>0.05 for all**)**, nor gabapentinoid use was (Supplementary Figure E-7**A-E,** P>0.05 for all) with speed, focus, or accuracy. Moreover, the number of current analgesia medications similarly was not association with NVT performance (Supplementary Figure E-8**A-E**, P>0.05 for all).



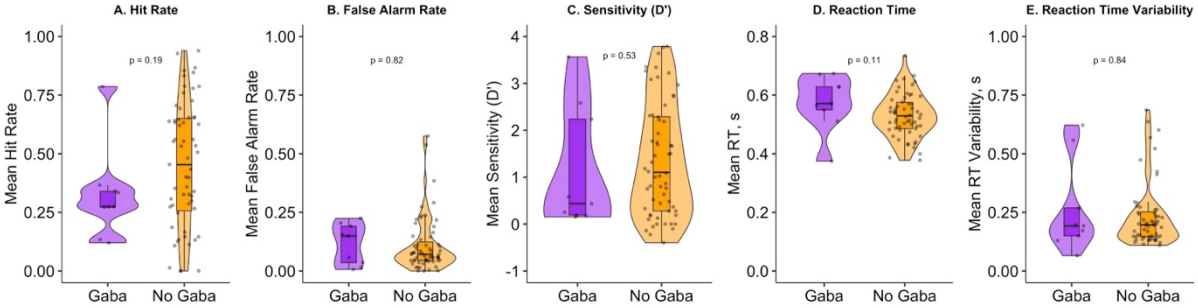
Supplementary Figure E-5. Opioid use does not affect task performance in fibromyalgia.

There was no association between self-reported current opioid use and speed, focus, or accuracy on the NVT. Each panel displays violin plots overlaid with box-and-whisker plots to illustrate the distribution of responses within each group. The central line represents the mean, with whiskers indicating ±1 standard deviation (SD). P-values are derived from independent t-tests comparing opioid vs no opioid groups for each NVT behavioural metric. FM, fibromyalgia. HC, RT, reaction time.



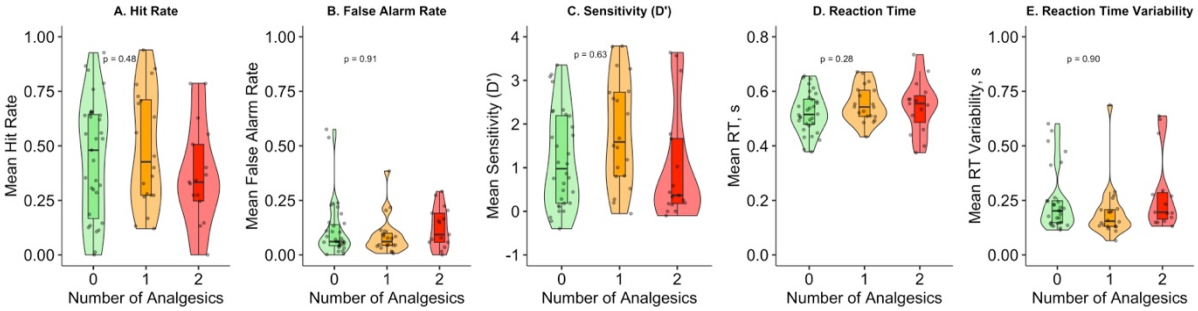
Supplementary Figure E-6. Tricyclic antidepressant use does not affect task performance in fibromyalgia.

There was no association between self-reported current tricyclic antidepressant use and speed, focus, or accuracy on the NVT. Each panel displays violin plots overlaid with box-and-whisker plots to illustrate the distribution of responses within each group. The central line represents the mean, with whiskers indicating ±1 standard deviation (SD). P-values are derived from independent t-tests comparing TCA vs no TCA groups for each NVT behavioural metric. FM, fibromyalgia. HC, RT, reaction time. TCA, tricyclic antidepressant.



Supplementary Figure E-7. Gabapentinoid use does not affect task performance in fibromyalgia.

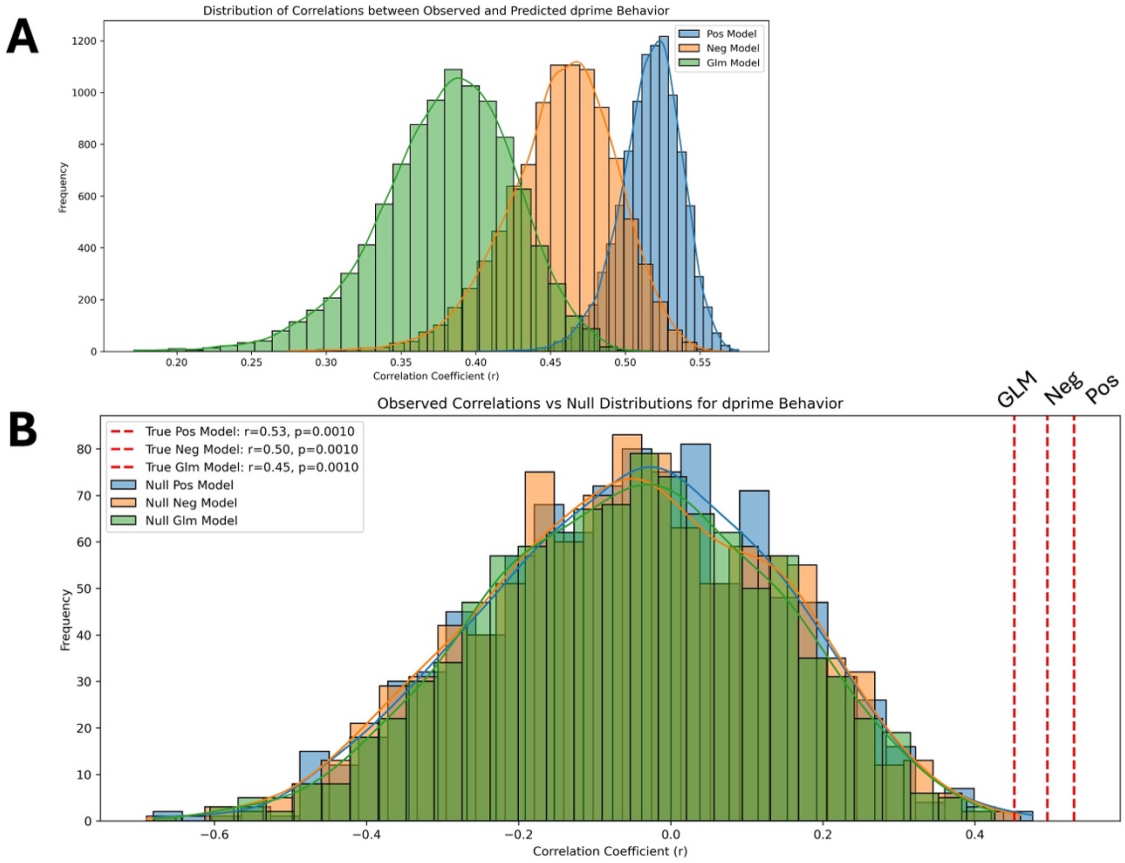
There was no association between self-reported current gabapentinoid use and speed, focus, or accuracy on the NVT. Each panel displays violin plots overlaid with box-and-whisker plots to illustrate the distribution of responses within each group. The central line represents the mean, with whiskers indicating ±1 standard deviation (SD). P-values are derived from independent t-tests comparing Gaba vs no Gaba groups for each NVT behavioural metric. FM, fibromyalgia. HC, RT, reaction time. Gaba, gabapentinoid.



Supplementary Figure E-8. Number of analgesia medications do not affect task performance in fibromyalgia.

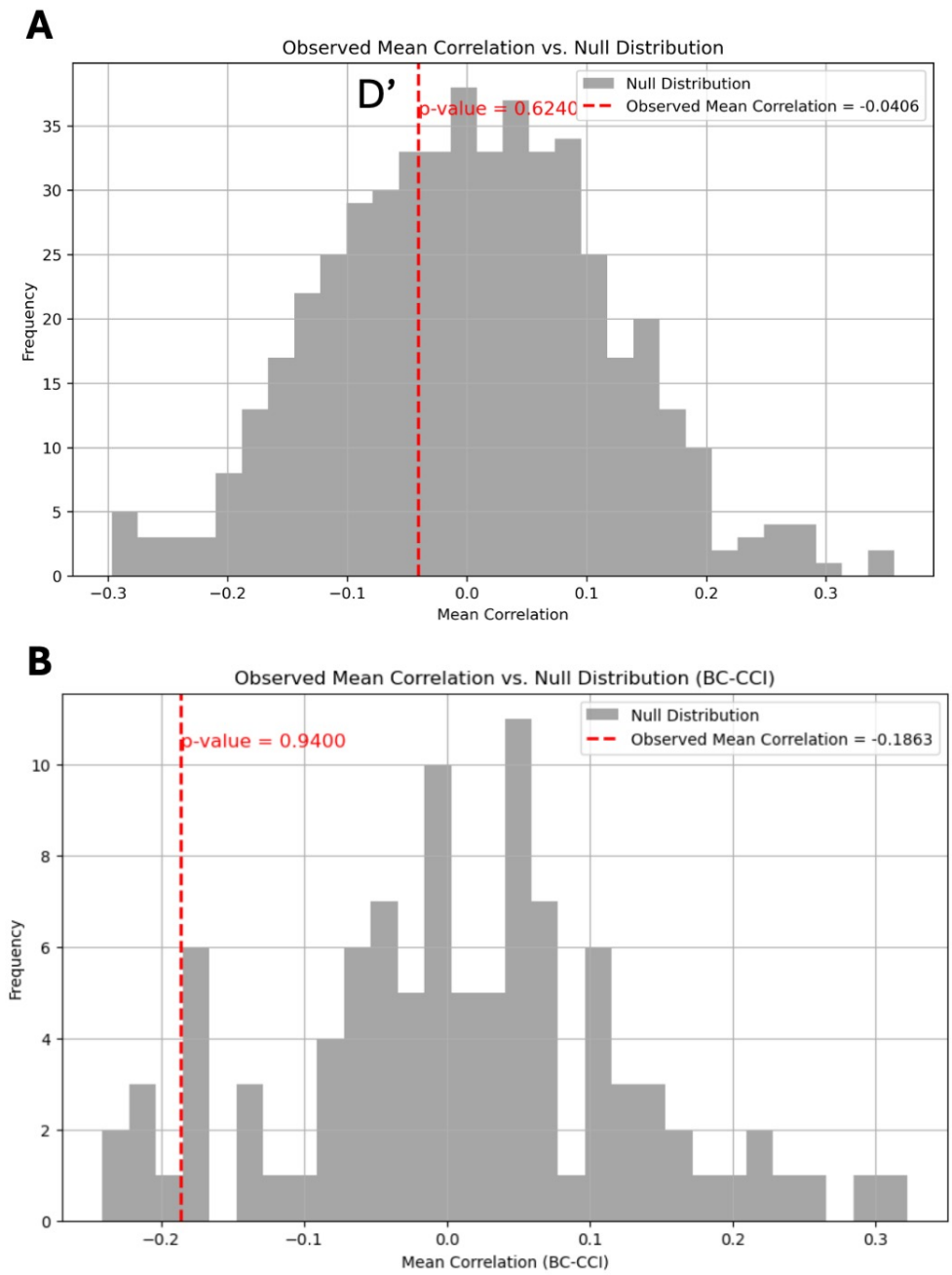
There was no association between the number of current analgesia medications taken and speed, focus, or accuracy on the NVT. Each panel displays violin plots overlaid with box-and-whisker plots to illustrate the distribution of responses within each group. The central line represents the mean, with whiskers indicating ±1 standard deviation (SD). P-values are derived from ANOVA comparing the number of medication groups for each NVT behavioural metric. FM, fibromyalgia. HC, RT, reaction time.

E.7 Objective 4: FM-saCPM



Supplementary Figure E-9. K-fold cross-validation and permutation testing of CPM.

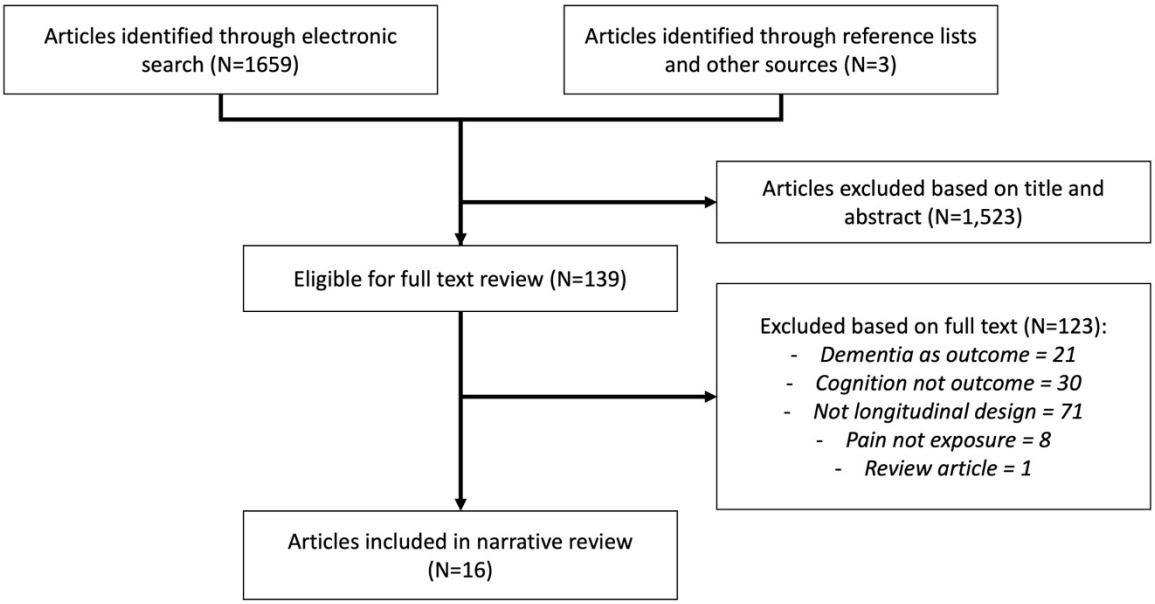
A. The distribution of correlation coefficients from K-fold cross-validation with 1,000 iterations B. The observed (red lines) vs null distribution of correlations (x-axis) from 10,000 permutations. Pos, High-attention model. Neg, Low-attention model. GLM, combined model.



Supplementary Figure E-10. Application of saCPM to predict sustained attention and subjective cognitive difficulties in fibromyalgia patients.

The saCPM defined by Rosenberg et al. (2016) does not predict sustained attention (A) in fibromyalgia patients. Although saCPM scores were negatively correlated with subjective cognitive difficulties (B), this relationship was not statistically significant. Higher values of D' indicate better sustained attention. Higher values of BC-CCI indicate more severe self-reported cognitive difficulties. D', task accuracy on Number Vigilance Task (NVT). BC-CCI, British Columbia Cognitive Complaints Inventory. Rho, Spearman's correlation. saCPM, sustained attention connectome predictive model (taken from Rosenberg et al., 2016).

F Appendix F: Introduction



Supplementary Figure F-1. Flow diagram for study selection for longitudinal studies examining the relationship between pain and cognitive decline

F.1 Search strategy for narrative review of longitudinal relationship between pain and cognitive decline

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Medline (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) 1946 to present

1 fibromyalgia/ 10592

2 chronic pain/ 26169

3 musculoskeletal pain/ 5072

4 (mult* adj3 pain).ti,ab. 19188

5 "presence of pain".ti,ab. 2605

6 (regional adj3 pain).ti,ab. 12338

7 (radicular adj pain).ti,ab. 4922

8 (joint adj pain).ti,ab. 14039

9 (chronic adj3 pain).ti,ab. 139018

10 fibromyalgia.ti,ab. 20845

11 (widespread adj3 pain).ti,ab. 4996

12 exp Low Back Pain/ or exp Chronic Pain/ or exp Complex Regional Pain Syndromes/ or exp Fibromyalgia/ or exp Nociceptive Pain/ 69041

13 pain/mo 130

14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 228669

15 Longitudinal Studies/ 179715

16 Cohort Studies/ 352434

17 Prospective Studies/ 706880

18 Retrospective Studies/ 1256596

19 Case-Control Studies/ or Epidemiologic Methods/ 373882

20 (observ* or cohort or prospectiv* or retrospectiv* or population or longitud* or community or case* control or cross* section*).ti,ab. 11651412

21 15 or 16 or 17 or 18 or 19 or 20 12235615

22 exp Cognition/ 214208

23 exp Mild Cognitive Impairment/ or exp Cognition Disorders/ 126405

24 memory disorders/ 25032

25 exp Executive Function/ or exp Neuropsychological Tests/ or exp Memory Disorders/ or exp Cognition Disorders/ 318127

26 cognition.ti. 35036

27 ((cognit* or neurocognit* or memory or neuropsy* or neuro*) adj (impair* or disorder* or dysfunction* or function* ag?ing or declin* or status or perform* or diabil* or disable* or maint* or enhanc*)).ti. 133429

28 ((maint* or impair* or disorder* or declin* or enhanc*) adj (cognit* or neurocognit* or memory or neuropsy* or neuro*)).ti. 8261

29 (amyloid or tau or plasticity).ti. 116080

30 mini mental state examination.ti,ab. 25973

31 mini mental state exam*.ti,ab. 27647

32 MMSE.ti,ab. 20669

33 MOCA.ti,ab. 8003

34 montreal cognitive assess*.ti,ab. 9299

35 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 715950

36 14 and 21 and 35 1659

8 References

[1] Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain (Guideline NG193): National Institute for Health and Care Excellence (NICE), 2021.

[2] National Institute for Health and Care Excellence: Guidelines. Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain. London: National Institute for Health and Care Excellence (NICE)
Copyright © NICE 2021., 2021.

[3] Adamczyk WM, Szikszay TM, Nahman-Averbuch H, Skalski J, Nastaj J, Gouverneur P, Luedtke K. To calibrate or not to calibrate? A methodological dilemma in experimental pain research. The journal of Pain 2022;23(11):1823-1832.

[4] Ahmed M, Aamir R, Jishi Z, Scharf MB. The Effects of Milnacipran on Sleep Disturbance in Fibromyalgia: A Randomized, Double-Blind, Placebo-Controlled, Two-Way Crossover Study. J Clin Sleep Med 2016;12(1):79-86.

[5] Alfaro-Almagro F. Image processing and quality control for the first 10,000 brain imaging datasets from UK Biobank. Neuroimage 2018;166.

[6] Alfaro-Almagro F. Brain imaging in UK Biobank: University of Oxford, 2020.

[7] Alfaro-Almagro F, McCarthy P, Afyouni S, Anderson JLR, Bastiani M, Miller KL, Nichols TE, Smith SM. Confound modelling in UK Biobank brain imaging. bioRxiv 2020:2020.2003.2011.987693.

[8] Alim-Marvasti A, Ciocca M, Kuleindiren N, Lin A, Selim H, Mahmud M. Subjective brain fog: a four-dimensional characterization in 25,796 participants. Frontiers in Human Neuroscience 2024;18:1409250.

[9] Alimoradi Z, Jafari E, Broström A, Ohayon MM, Lin C-Y, Griffiths MD, Blom K, Jernelöv S, Kaldo V, Pakpour AH. Effects of cognitive behavioral therapy for insomnia (CBT-I) on quality of life: A systematic review and meta-analysis. Sleep Medicine Reviews 2022;64:101646.

[10] Allen NE, Sudlow C, Peakman T, Collins R. UK biobank data: come and get it. Sci Transl Med 2014;6(224):224ed224.

[11] Altman DG. Comparability of randomised groups. Journal of the Royal Statistical Society Series D: The Statistician 1985;34(1):125-136.

[12] Anderson TW. An Introduction to Multivariate Statistical Analysis, 2nd Edition, Vol. 41: Biometric Society, 1985. pp. 815-815.

[13] Andersson JL, Jenkinson M, Smith S. Non-linear registration, aka Spatial normalisation FMRIB technical report TR07JA2. FMRIB Analysis Group of the University of Oxford 2007;2(1):1-22.

[14] Andrews P, Steultjens M, Riskowski J. Chronic widespread pain prevalence in the general population: A systematic review. Eur J Pain 2018;22(1):5-18.

[15] Arnold LM, Bennett RM, Crofford LJ, Dean LE, Clauw DJ, Goldenberg DL, Fitzcharles MA, Paiva ES, Staud R, Sarzi-Puttini P, Buskila D, Macfarlane GJ. AAPT Diagnostic Criteria for Fibromyalgia. J Pain 2019;20(6):611-628.

[16] Arnold LM, Chatamra K, Hirsch I, Stoker M. Safety and efficacy of esreboxetine in patients with fibromyalgia: An 8-week, multicenter, randomized, double-blind, placebo-controlled study. Clin Ther 2010;32(9):1618-1632.

[17] Arnold LM, Goldenberg DL, Stanford SB, Lalonde JK, Sandhu HS, Keck PE, Jr., Welge JA, Bishop F, Stanford KE, Hess EV, Hudson JI. Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. Arthritis Rheum 2007;56(4):1336-1344.

[18] Arnold LM, Russell IJ, Diri EW, Duan WR, Young JP, Jr., Sharma U, Martin SA, Barrett JA, Haig G. A 14-week, randomized, double-blinded, placebo-controlled monotherapy trial of pregabalin in patients with fibromyalgia. J Pain 2008;9(9):792-805.

[19] Arthritis V. Fibromyalgia. United Kingdom, 2020.

[20] Asmundson GJG, Katz J. Understanding the co-occurrence of anxiety disorders and chronic pain: state-of-the-art. Depression and Anxiety 2009;26(10):888-901.

[21] Baggetta P, Alexander PA. Conceptualization and operationalization of executive function. Mind, Brain, and Education 2016;10(1):10-33.

[22] Bair MJ, Krebs EE. Fibromyalgia. Ann Intern Med 2020;172(5):Itc33-itc48.

[23] Baker KS, Gibson S, Georgiou-Karistianis N, Roth RM, Giummarra MJ. Everyday Executive Functioning in Chronic Pain: Specific Deficits in Working Memory and Emotion Control, Predicted by Mood, Medications, and Pain Interference. The Clinical journal of pain 2016;32(8):673-680.

[24] Baker KS, Gibson SJ, Georgiou-Karistianis N, Giummarra MJ. Relationship between self-reported cognitive difficulties, objective neuropsychological test performance and psychological distress in chronic pain. Eur J Pain 2018;22(3):601-613.

[25] Baliki MN, Mansour AR, Baria AT, Apkarian AV. Functional reorganization of the default mode network across chronic pain conditions. PLoS One 2014;9(9):e106133.

[26] Ballesio A, Aquino M, Kyle SD, Ferlazzo F, Lombardo C. Executive Functions in Insomnia Disorder: A Systematic Review and Exploratory Meta-Analysis. Front Psychol 2019;10:101.

[27] Bannister K. Descending pain modulation: influence and impact. Current Opinion in Physiology 2019;11:62-66.

[28] Baraniuk JN, Whalen G, Cunningham J, Clauw DJ. Cerebrospinal fluid levels of opioid peptides in fibromyalgia and chronic low back pain. BMC Musculoskelet Disord 2004;5:48.

[29] Baron RM, Kenny DA. The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. Journal of personality and social psychology 1986;51(6):1173.

[30] Baroncini M, Jissendi P, Balland E, Besson P, Pruvo JP, Francke JP, Dewailly D, Blond S, Prevot V. MRI atlas of the human hypothalamus. Neuroimage 2012;59(1):168-180.

[31] Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep medicine 2001;2(4):297-307.

[32] Bathgate CJ, Edinger JD, Krystal AD. Insomnia patients with objective short sleep duration have a blunted response to cognitive behavioral therapy for insomnia. Sleep 2017;40(1):zsw012.

[33] Bédard MA, Montplaisir J, Richer F, Rouleau I, Malo J. Obstructive sleep apnea syndrome: pathogenesis of neuropsychological deficits. J Clin Exp Neuropsychol 1991;13(6):950-964.

[34] Behrens TE, Woolrich MW, Jenkinson M, Johansen-Berg H, Nunes RG, Clare S, Matthews PM, Brady JM, Smith SM. Characterization and propagation of uncertainty in diffusion-weighted MR imaging. Magn Reson Med 2003;50(5):1077-1088.

[35] Beiner E, Lucas V, Reichert J, Buhai D-V, Jesinghaus M, Vock S, Drusko A, Baumeister D, Eich W, Friederich H-C, Tesarz J. Stress biomarkers in individuals with fibromyalgia syndrome: a systematic review with meta-analysis. PAIN 2023;164(7):1416-1427.

[36] Bell T, Franz CE, Kremen WS. Persistence of pain and cognitive impairment in older adults. J Am Geriatr Soc 2022;70(2):449-458.

[37] Bell T, Franz CE, Kremen WS. Persistence of pain and cognitive impairment in older adults. Journal of the American Geriatrics Society 2022;70(2):449-458.
[38] Bell T, Trost Z, Buelow MT, Clay O, Younger J, Moore D, Crowe M. Meta-analysis of cognitive performance in fibromyalgia. J Clin Exp Neuropsychol 2018;40(7):698-714.
[39] Bell TR, Pope CN, Downer B, Barba C, Crowe M. Pain associates with subjective memory problems and cognition in older Puerto Rican adults. Aging, Neuropsychology, and Cognition 2022;29(6):985-999.
[40] Bell TR, Sprague BN, Ross LA. Longitudinal associations of pain and cognitive decline in community-dwelling older adults. Psychol Aging 2022;37(6):715-730.
[41] Bennett R, Nelson D. Cognitive behavioral therapy for fibromyalgia. Nature Clinical Practice Rheumatology 2006;2(8):416-424.
[42] Bennett RM, Bushmakin AG, Cappelleri JC, Zlateva G, Sadosky AB. Minimal clinically important difference in the fibromyalgia impact questionnaire. J Rheumatol 2009;36(6):1304-1311.
[43] Bennett RM, Friend R, Jones KD, Ward R, Han BK, Ross RL. The Revised Fibromyalgia Impact Questionnaire (FIQR): validation and psychometric properties. Arthritis Res Ther 2009;11(4):R120.
[44] Bennett RM, Kamin M, Karim R, Rosenthal N. Tramadol and acetaminophen combination tablets in the treatment of fibromyalgia pain: a double-blind, randomized, placebo-controlled study. Am J Med 2003;114(7):537-545.
[45] Berna C, Leknes S, Holmes EA, Edwards RR, Goodwin GM, Tracey I. Induction of Depressed Mood Disrupts Emotion Regulation Neurocircuitry and Enhances Pain Unpleasantness. Biological Psychiatry 2010;67(11):1083-1090.
[46] Bernardy K, Füber N, Köllner V, Häuser W. Efficacy of cognitive-behavioral therapies in fibromyalgia syndrome—a systematic review and metaanalysis of randomized controlled trials. The journal of Rheumatology 2010;37(10):1991-2005.
[47] Berrar D. Cross-validation, 2019.
[48] Berryman C, Stanton TR, Bowering KJ, Tabor A, McFarlane A, Moseley GL. Do people with chronic pain have impaired executive function? A meta-analytical review. Clin Psychol Rev 2014;34(7):563-579.
[49] Berryman C, Stanton TR, Jane Bowering K, Tabor A, McFarlane A, Lorimer Moseley G. Evidence for working memory deficits in chronic pain: a systematic review and meta-analysis. Pain 2013;154(8):1181-1196.
[50] Berwick R, Barker C, Goebel A. The diagnosis of fibromyalgia syndrome. Clin Med (Lond) 2022;22(6):570-574.
[51] Bicego A, Monseur J, Rousseaux F, Faymonville ME, Malaise N, Salamun I, Collinet A, Nyssen AS, Vanhaudenhuyse A. Drop-out from chronic pain treatment programmes: Is randomization justified in biopsychosocial approaches? J Rehabil Med 2021;53(4):jrm00185.
[52] Binnekade TT, Scherder EJA, Maier AB, Lobbezoo F, Overdorp EJ, Rhebergen D, Perez R, Oosterman JM. Pain in Patients with Different Dementia Subtypes, Mild Cognitive Impairment, and Subjective Cognitive Impairment. Pain Med 2018;19(5):920-927.
[53] Bjurstrom MF, Irwin MR. Polysomnographic characteristics in nonmalignant chronic pain populations: A review of controlled studies. Sleep Medicine Reviews 2016;26:74-86.
[54] Bollen KA. The Consequences of Measurement Error. Structural Equations with Latent Variables, 1989. pp. 151-178.
[55] Bollen KA. Structural equations with latent variables: John Wiley & Sons, 2014.
[56] Bonaz B, Lane RD, Oshinsky ML, Kenny PJ, Sinha R, Mayer EA, Critchley HD. Diseases, Disorders, and Comorbidities of Interoception. Trends in Neurosciences 2021;44(1):39-51.
[57] Bosma RL, Mojarad EA, Leung L, Pukall C, Staud R, Stroman PW. FMRI of spinal and supra-spinal correlates of temporal pain summation in fibromyalgia patients. Hum Brain Mapp 2016;37(4):1349-1360.
[58] Bostock S, Luik AI, Espie CA. Sleep and Productivity Benefits of Digital Cognitive Behavioral Therapy for Insomnia: A Randomized Controlled Trial Conducted in the Workplace Environment. J Occup Environ Med 2016;58(7):683-689.
[59] Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, Cunin G, Fermanian J, Ginies P, Grun-Overdyking A, Jafari-Schluep H, Lantéri-Minet M, Laurent B, Mick G, Serrie A, Valade D, Vicaut E. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain 2005;114(1-2):29-36.
[60] Boyle J, Eriksson MEV, Gribble L, Gouni R, Johnsen S, Coppini DV, Kerr D. Randomized, Placebo-Controlled Comparison of Amitriptyline, Duloxetine, and Pregabalin in Patients With Chronic Diabetic Peripheral Neuropathic Pain: Impact on pain, polysomnographic sleep, daytime functioning, and quality of life. Diabetes Care 2012;35(12):2451-2458.
[61] Branco J, Atalaia A, Paiva T. Sleep cycles and alpha-delta sleep in fibromyalgia syndrome. The Journal of rheumatology 1994;21(6):1113-1117.
[62] Branco JC, Zachrisson O, Perrot S, Mainguy Y. A European multicenter randomized double-blind placebo-controlled monotherapy clinical trial of milnacipran in treatment of fibromyalgia. J Rheumatol 2010;37(4):851-859.
[63] Braz AS, Morais LC, Paula AP, Diniz MF, Almeida RN. Effects of Panax ginseng extract in patients with fibromyalgia: a 12-week, randomized, double-blind, placebo-controlled trial. Braz J Psychiatry 2013;35(1):21-28.
[64] Brown SC, Glass JM, Park DC. The relationship of pain and depression to cognitive function in rheumatoid arthritis patients. Pain 2002;96(3):279-284.
[65] Brummett CM, Janda AM, Schueller CM, Tsodikov A, Morris M, Williams DA, Clauw DJ. Survey criteria for fibromyalgia independently predict increased postoperative opioid consumption after lower-extremity joint arthroplasty: a prospective, observational cohort study. Anesthesiology 2013;119(6):1434-1443.
[66] Burfield AH, Wan TTH, Sole ML, Cooper JW. Behavioral cues to expand a pain model of the cognitively impaired elderly in long-term care. Clinical interventions in aging 2012;7:207-223.
[67] Burgmer M, Gaubitz M, Konrad C, Wrenger M, Hilgart S, Heuft G, Pfleiderer B. Decreased gray matter volumes in the cingulo-frontal cortex and the amygdala in patients with fibromyalgia. Psychosom Med 2009;71(5):566-573.
[68] Burmester B, Leathem J, Merrick P. Subjective Cognitive Complaints and Objective Cognitive Function in Aging: A Systematic Review and Meta-Analysis of Recent Cross-Sectional Findings. Neuropsychology Review 2016;26(4):376-393.
[69] Buysse DJ, Reynolds III CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry research 1989;28(2):193-213.
[70] Caracciolo B, Gatz M, Xu W, Pedersen NL, Fratiglioni L. Differential distribution of subjective and objective cognitive impairment in the population: a nation-wide twin-study. Journal of Alzheimer's Disease 2012;29(2):393-403.
[71] Carette S, Bell MJ, Reynolds WJ, Haraoui B, McCain GA, Bykerk VP, Edworthy SM, Baron M, Koehler BE, Fam AG, et al. Comparison of amitriptyline, cyclobenzaprine, and placebo in the treatment of fibromyalgia. A randomized, double-blind clinical trial. Arthritis Rheum 1994;37(1):32-40.

[72] Carette S, Oakson G, Guimont C, Steriade M. Sleep electroencephalography and the clinical response to amitriptyline in patients with fibromyalgia. Arthritis Rheum 1995;38(9):1211-1217.
[73] Carney CE, Buysse DJ, Ancoli-Israel S, Edinger JD, Krystal AD, Lichstein KL, Morin CM. The consensus sleep diary: standardizing prospective sleep self-monitoring. Sleep 2012;35(2):287-302.
[74] Carpenter J, Kenward M. Missing data in randomised controlled trials: a practical guide. Birmingham, 2007.
[75] Carver CS, White TL. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: the BIS/BAS scales. Journal of personality and social psychology 1994;67(2):319.
[76] Castel A, Cascón R, Padrol A, Sala J, Rull M. Multicomponent cognitive-behavioral group therapy with hypnosis for the treatment of fibromyalgia: long-term outcome. J Pain 2012;13(3):255-265.
[77] Castellanos FX, Sonuga-Barke EJS, Milham MP, Tannock R. Characterizing cognition in ADHD: beyond executive dysfunction. Trends in Cognitive Sciences 2006;10(3):117-123.
[78] Cella M, Chalder T. Measuring fatigue in clinical and community settings. Journal of psychosomatic research 2010;69(1):17-22.
[79] Cha DS, Carmona NE, Mansur RB, Lee Y, Park HJ, Rodrigues NB, Subramaniapillai M, Rosenblat JD, Pan Z, Lee JH, Lee J, Almatham F, Alageel A, Shekotikhina M, Zhou AJ, Rong C, Harrison J, McIntyre RS. Pain and major depressive disorder: Associations with cognitive impairment as measured by the THINC-integrated tool (THINC-it). Scand J Pain 2017;15:62-67.
[80] Chen FF. Sensitivity of goodness of fit indexes to lack of measurement invariance. Structural equation modeling: a multidisciplinary journal 2007;14(3):464-504.
[81] Chen PY, Jan YW, Yang CM. Are the Insomnia Severity Index and Pittsburgh Sleep Quality Index valid outcome measures for Cognitive Behavioral Therapy for Insomnia? Inquiry from the perspective of response shifts and longitudinal measurement invariance in their Chinese versions. Sleep Med 2017;35:35-40.
[82] Chen Q, Heinricher MM. Shifting the Balance: How Top-Down and Bottom-Up Input Modulate Pain via the Rostral Ventromedial Medulla. Front Pain Res (Lausanne) 2022;3:932476.
[83] Cheng JC, Anzolin A, Berry M, Honari H, Paschali M, Lazaridou A, Lee J, Ellingsen DM, Loggia ML, Grahl A, Lindquist MA, Edwards RR, Napadow V. Dynamic Functional Brain Connectivity Underlying Temporal Summation of Pain in Fibromyalgia. Arthritis Rheumatol 2022;74(4):700-710.
[84] Cheng P, Luik AI, Fellman-Couture C, Peterson E, Joseph CLM, Tallent G, Tran KM, Ahmedani BK, Roehrs T, Roth T, Drake CL. Efficacy of digital CBT for insomnia to reduce depression across demographic groups: a randomized trial. Psychol Med 2019;49(3):491-500.
[85] Cheung GW, Lau RS. Testing Mediation and Suppression Effects of Latent Variables:Bootstrapping With Structural Equation Models. Organizational Research Methods 2008;11(2):296-325.
[86] Cheung GW, Rensvold RB. Evaluating goodness-of-fit indexes for testing measurement invariance. Structural equation modeling 2002;9(2):233-255.
[87] Chong PLH, Garic D, Shen MD, Lundgaard I, Schwichtenberg AJ. Sleep, cerebrospinal fluid, and the glymphatic system: A systematic review. Sleep Medicine Reviews 2022;61:101572.
[88] Choy EHS. The role of sleep in pain and fibromyalgia. Nature Reviews Rheumatology 2015;11(9):513-520.
[89] Chun MM, Golomb JD, Turk-Browne NB. A taxonomy of external and internal attention. Annu Rev Psychol 2011;62:73-101.
[90] Cieslik EC, Zilles K, Caspers S, Roski C, Kellermann TS, Jakobs O, Langner R, Laird AR, Fox PT, Eickhoff SB. Is There "One" DLPFC in Cognitive Action Control? Evidence for Heterogeneity From Co-Activation-Based Parcellation. Cerebral Cortex 2012;23(11):2677-2689.
[91] Cifre I, Sitges C, Fraiman D, Muñoz M, Balenzuela P, González-Roldán A, Martínez-Jauand M, Birbaumer N, Chialvo DR, Montoya P. Disrupted functional connectivity of the pain network in fibromyalgia. Psychosom Med 2012;74(1):55-62.
[92] Cipriani A, Ostinelli EG, Cowen PJ. Pharmacological interventions for insomnia disorder in adults - Authors' reply. Lancet 2022;400(10366):1846.
[93] Clauw D. Hijacking the endogenous opioid system to treat pain: who thought it would be so complicated? Pain 2017;158(12):2283-2284.
[94] Clauw DJ. Fibromyalgia: a clinical review. Jama 2014;311(15):1547-1555.
[95] Clauw DJ, Mease P, Palmer RH, Gendreau RM, Wang Y. Milnacipran for the treatment of fibromyalgia in adults: a 15-week, multicenter, randomized, double-blind, placebo-controlled, multiple-dose clinical trial. Clin Ther 2008;30(11):1988-2004.
[96] Clifton L, Birks J, Clifton DA. Comparing different ways of calculating sample size for two independent means: A worked example. Contemp Clin Trials Commun 2019;13:100309.
[97] Clifton L, Clifton DA. The correlation between baseline score and post-intervention score, and its implications for statistical analysis. Trials 2019;20(1):43.
[98] Climent-Sanz C, Valenzuela-Pascual F, Martínez-Navarro O, Blanco-Blanco J, Rubí-Carnacea F, García-Martínez E, Soler-González J, Barallat-Gimeno E, Gea-Sánchez M. Cognitive behavioral therapy for insomnia (CBT-i) in patients with fibromyalgia: a systematic review and meta-analysis. Disabil Rehabil 2022;44(20):5770-5783.
[99] Cohen M, Quintner J, Weisman A. "Nociplastic Pain": A Challenge to Nosology and to Nociception. The Journal of Pain 2023;24(12):2131-2139.
[100] Cole MW, Ito T, Bassett DS, Schultz DH. Activity flow over resting-state networks shapes cognitive task activations. Nat Neurosci 2016;19(12):1718-1726.
[101] Collins R, Bowman L, Landray M, Peto R. The magic of randomization versus the myth of real-world evidence, Vol. 382: Massachusetts Medical Society, 2020. pp. 674-678.
[102] Conley S, Knies A, Batten J, Ash G, Miner B, Hwang Y, Jeon S, Redeker NS. Agreement between actigraphic and polysomnographic measures of sleep in adults with and without chronic conditions: A systematic review and meta-analysis. Sleep Medicine Reviews 2019;46:151-160.
[103] Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. Nature Reviews Neuroscience 2002;3(3):201-215.
[104] Cornelis MC, Wang Y, Holland T, Agarwal P, Weintraub S, Morris MC. Age and cognitive decline in the UK Biobank. PLoS One 2019;14(3):e0213948.
[105] Coulombe MA, Lawrence KS, Moulin DE, Morley-Forster P, Shokouhi M, Nielson WR, Davis KD. Lower Functional Connectivity of the Periaqueductal Gray Is Related to Negative Affect and Clinical Manifestations of Fibromyalgia. Front Neuroanat 2017;11:47.
[106] Craft RM. Modulation of pain by estrogens. Pain 2007;132 Suppl 1:S3-S12.

[107] Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, Pratt M, Ekelund U, Yngve A, Sallis JF. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003;35(8):1381-1395.
[108] Crawford JR, Garthwaite PH. Percentiles please: The case for expressing neuropsychological test scores and accompanying confidence limits as percentile ranks. The Clinical Neuropsychologist 2009;23(2):193-204.
[109] Crawford MR, Luik AI, Espie CA, Taylor HL, Burgess HJ, Jones AL, Team RUSR, Ong JC. Digital cognitive behavioral therapy for insomnia in women with chronic migraines. Headache: the journal of head and face pain 2020;60(5):902-915.
[110] Creed F. The risk factors for self-reported fibromyalgia with and without multiple somatic symptoms: The Lifelines cohort study. J Psychosom Res 2022;155:110745.
[111] Crofford LJ, Mease PJ, Simpson SL, Young JP, Jr., Martin SA, Haig GM, Sharma U. Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM): a 6-month, double-blind, placebo-controlled trial with pregabalin. Pain 2008;136(3):419-431.
[112] Crofford LJ, Rowbotham MC, Mease PJ, Russell IJ, Dworkin RH, Corbin AE, Young JP, Jr., LaMoreaux LK, Martin SA, Sharma U. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2005;52(4):1264-1273.
[113] Crow M, Denk F, McMahon SB. Genes and epigenetic processes as prospective pain targets. Genome Med 2013;5(2):12.
[114] Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, Thomas J. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev 2019;10(10):Ed000142.
[115] Curtis AF, Williams JM, McCoy KJM, McCrae CS. Chronic Pain, Sleep, and Cognition in Older Adults With Insomnia: A Daily Multilevel Analysis. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine 2018;14(10):1765-1772.
[116] D'Agnelli S, Arendt-Nielsen L, Gerra MC, Zatorri K, Boggiani L, Baciarello M, Bignami E. Fibromyalgia: Genetics and epigenetics insights may provide the basis for the development of diagnostic biomarkers. Mol Pain 2019;15:1744806918819944.
[117] D'Onghia M, Ciaffi J, Lisi L, Mancarella L, Ricci S, Stefanelli N, Meliconi R, Ursini F. Fibromyalgia and obesity: A comprehensive systematic review and meta-analysis. Seminars in Arthritis and Rheumatism 2021;51(2):409-424.
[118] Dailey DL, Keffala VJ, Sluka KA. Do cognitive and physical fatigue tasks enhance pain, cognitive fatigue, and physical fatigue in people with fibromyalgia? Arthritis Care Res (Hoboken) 2015;67(2):288-296.
[119] Daoust R, Paquet J, Williamson D, Perry JJ, Iseppon M, Castonguay V, Morris J, Cournoyer A. Accuracy of a self-report prescription opioid use diary for patients discharge from the emergency department with acute pain: a multicentre prospective cohort study. BMJ Open 2022;12(10):e062984.
[120] Davidson JR, Dickson C, Han H. Cognitive behavioural treatment for insomnia in primary care: a systematic review of sleep outcomes. Br J Gen Pract 2019;69(686):e657-e664.
[121] Deco G, Ponce-Alvarez A, Mantini D, Romani GL, Hagmann P, Corbetta M. Resting-State Functional Connectivity Emerges from Structurally and Dynamically Shaped Slow Linear Fluctuations. The Journal of Neuroscience 2013;33(27):11239-11252.
[122] Delgado-Alonso C, Díez-Cirarda M, Pagán J, Pérez-Izquierdo C, Oliver-Mas S, Fernández-Romero L, Martínez-Petit Á, Valles-Salgado M, Gil-Moreno MJ, Yus M. Unraveling brain fog in post-COVID syndrome: relationship between subjective cognitive complaints and cognitive function, fatigue, and neuropsychiatric symptoms. European Journal of Neurology 2023.
[123] Denk F, McMahon SB, Tracey I. Pain vulnerability: a neurobiological perspective. Nat Neurosci 2014;17(2):192-200.
[124] Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 2006;31(3):968-980.
[125] Diatchenko L, Fillingim RB, Smith SB, Maixner W. The phenotypic and genetic signatures of common musculoskeletal pain conditions. Nature Reviews Rheumatology 2013;9(6):340-350.
[126] Dick B, Eccleston C, Crombez G. Attentional functioning in fibromyalgia, rheumatoid arthritis, and musculoskeletal pain patients. Arthritis Rheum 2002;47(6):639-644.
[127] Dick BD, Verrier MJ, Harker KT, Rashiq S. Disruption of cognitive function in fibromyalgia syndrome. Pain 2008;139(3):610-616.
[128] Doran SM, Van Dongen HP, Dinges DF. Sustained attention performance during sleep deprivation: evidence of state instability. Archives italiennes de biologie 2001;139(3):253-267.
[129] Drewes AM, Andreasen A, Jennum P, Nielsen KD. Zopiclone in the treatment of sleep abnormalities in fibromyalgia. Scand J Rheumatol 1991;20(4):288-293.
[130] Drummond SP, Anderson DE, Straus LD, Vogel EK, Perez VB. The effects of two types of sleep deprivation on visual working memory capacity and filtering efficiency. PloS one 2012;7(4):e35653.
[131] Drummond SP, Paulus MP, Tapert SF. Effects of two nights sleep deprivation and two nights recovery sleep on response inhibition. Journal of sleep research 2006;15(3):261-265.
[132] Drummond SPA, Bischoff-Grethe A, Dinges DF, Ayalon L, Mednick SC, Meloy MJ. The Neural Basis of the Psychomotor Vigilance Task. Sleep 2005;28(9):1059-1068.
[133] Dzierzewski JM, Martin JL, Fung CH, Song Y, Fiorentino L, Jouldjian S, Rodriguez JC, Mitchell M, Josephson K, Alessi CA. CBT for late-life insomnia and the accuracy of sleep and wake perceptions: Results from a randomized-controlled trial. Journal of Sleep Research 2019;28(4):e12809.
[134] Edinger JD, Wohlgemuth WK, Krystal AD, Rice JR. Behavioral insomnia therapy for fibromyalgia patients: a randomized clinical trial. Archives of internal medicine 2005;165(21):2527-2535.
[135] Egbewale BE, Lewis M, Sim J. Bias, precision and statistical power of analysis of covariance in the analysis of randomized trials with baseline imbalance: a simulation study. BMC Medical Research Methodology 2014;14(1):49.
[136] Eich W, Bär KJ, Bernateck M, Burgmer M, Dexl C, Petzke F, Sommer C, Winkelmann A, Häuser W. [Definition, classification, clinical diagnosis and prognosis of fibromyalgia syndrome : Updated guidelines 2017 and overview of systematic review articles]. Schmerz 2017;31(3):231-238.
[137] Elkana O, Falcofsky AK, Shorer R, Bar-On Kalfon T, Ablin JN. Does the cognitive index of the symptom severity scale evaluate cognition? Data from subjective and objective cognitive measures in fibromyalgia. Clinical and experimental rheumatology 2019;37 Suppl 116(1):51-57.

[138] Ellingsen DM, Beissner F, Moher Alsady T, Lazaridou A, Paschali M, Berry M, Isaro L, Grahl A, Lee J, Wasan AD, Edwards RR, Napadow V. A picture is worth a thousand words: linking fibromyalgia pain widespreadness from digital pain drawings with pain catastrophizing and brain cross-network connectivity. Pain 2021;162(5):1352-1363.
[139] Espie CA, Emsley R, Kyle SD, Gordon C, Drake CL, Siriwardena AN, Cape J, Ong JC, Sheaves B, Foster R, Freeman D, Costa-Font J, Marsden A, Luik AI. Effect of Digital Cognitive Behavioral Therapy for Insomnia on Health, Psychological Well-being, and Sleep-Related Quality of Life: A Randomized Clinical Trial. JAMA Psychiatry 2019;76(1):21-30.
[140] Espie CA, Kyle SD, Hames P, Gardani M, Fleming L, Cape J. The Sleep Condition Indicator: a clinical screening tool to evaluate insomnia disorder. BMJ Open 2014;4(3):e004183.
[141] Espie CA, Kyle SD, Williams C, Ong JC, Douglas NJ, Hames P, Brown JS. A randomized, placebo-controlled trial of online cognitive behavioral therapy for chronic insomnia disorder delivered via an automated media-rich web application. Sleep 2012;35(6):769-781.
[142] Esterman M, Noonan SK, Rosenberg M, Degutis J. In the zone or zoning out? Tracking behavioral and neural fluctuations during sustained attention. Cereb Cortex 2013;23(11):2712-2723.
[143] Esterman M, Rothlein D. Models of sustained attention. Current opinion in psychology 2019;29:174-180.
[144] Etnier JL, Karper WB, Gapin JI, Barella LA, Chang YK, Murphy KJ. Exercise, fibromyalgia, and fibrofog: a pilot study. Journal of physical activity & health 2009;6(2):239-246.
[145] Evoy KE, Morrison MD, Saklad SR. Abuse and Misuse of Pregabalin and Gabapentin. Drugs 2017;77(4):403-426.
[146] Ezra M, Faull OK, Jbabdi S, Pattinson KT. Connectivity-based segmentation of the periaqueductal gray matter in human with brainstem optimized diffusion MRI. Hum Brain Mapp 2015;36(9):3459-3471.
[147] Ezzati A, Wang C, Katz MJ, Derby CA, Zammit AR, Zimmerman ME, Pavlovic JM, Sliwinski MJ, Lipton RB. The Temporal Relationship between Pain Intensity and Pain Interference and Incident Dementia. Current Alzheimer research 2019;16(2):109-115.
[148] Fairweather DB, Kerr JS, Harrison DA, Moon CA, Hindmarch I. A double blind comparison of the effects of fluoxetine and amitriptyline on cognitive function in elderly depressed patients. Human Psychopharmacology: Clinical and Experimental 1993;8(1):41-47.
[149] Fang SC, Wu YL, Chen SC, Teng HW, Tsai PS. Subjective sleep quality as a mediator in the relationship between pain severity and sustained attention performance in patients with fibromyalgia. J Sleep Res 2019;28(6):e12843.
[150] Faull OK, Pattinson KTS. The cortical connectivity of the periaqueductal gray and the conditioned response to the threat of breathlessness. eLife 2017;6:e21749.
[151] Fawns-Ritchie C, Deary IJ. Reliability and validity of the UK Biobank cognitive tests. PLoS One 2020;15(4):e0231627.
[152] Fayaz A, Croft P, Langford R, Donaldson L, Jones G. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. BMJ open 2016;6(6):e010364.
[153] Fayaz A, Croft P, Langford RM, Donaldson LJ, Jones GT. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. BMJ Open 2016;6(6):e010364.
[154] Ficca G, Axelsson J, Mollicone DJ, Muto V, Vitiello MV. Naps, cognition and performance. Sleep Medicine Reviews 2010;14(4):249-258.
[155] Fields H, Heinricher MM. Anatomy and physiology of a nociceptive modulatory system. Philosophical Transactions of the Royal Society of London B, Biological Sciences 1985;308(1136):361-374.
[156] Fields HL, Heinricher MM, Mason P. Neurotransmitters in nociceptive modulatory circuits. Annu Rev Neurosci 1991;14(1):219-245.
[157] Finn ES, Shen X, Scheinost D, Rosenberg MD, Huang J, Chun MM, Papademetris X, Constable RT. Functional connectome fingerprinting: identifying individuals using patterns of brain connectivity. Nat Neurosci 2015;18(11):1664-1671.
[158] Fitzcharles M-A, Brachaniec M, Cooper L, Dubin R, Flynn T, Gerhold K, Häuser W, Cowan K, Laupacis A, Marleau R, Milot M, Szajcz-Keller N, Sumpton J, Walsh Z, El-Gabalawy H. A paradigm change to inform fibromyalgia research priorities by engaging patients and health care professionals. Canadian Journal of Pain 2017;1(1):137-147.
[159] Fitzcharles MA, Cohen SP, Clauw DJ, Littlejohn G, Usui C, Hauser W. Nociplastic pain: towards an understanding of prevalent pain conditions. Lancet 2021;397(10289):2098-2110.
[160] Fleming MK, Smejka T, Macey E, Luengo-Fernandez R, Henry AL, Robinson B, Kyle SD, Espie CA, Johansen-Berg H. Improving sleep after stroke: A randomised controlled trial of digital cognitive behavioural therapy for insomnia. Journal of Sleep Research 2024;33(2):e13971.
[161] Foley P, Kong Y, Dirvanskiene R, Valdes-Hernandez M, Bastiani M, Murnane J, Sellar R, Roberts N, Pernet C, Weir C. Coupling cognitive and brainstem dysfunction in multiple sclerosis-related chronic neuropathic limb pain. Brain communications 2022;4(3):fcac124.
[162] Fordham B, Sugavanam T, Edwards K, Hemming K, Howick J, Copsey B, Lee H, Kaidesoja M, Kirtley S, Hopewell S, das Nair R, Howard R, Stallard P, Hamer-Hunt J, Cooper Z, Lamb SE. Cognitive-behavioural therapy for a variety of conditions: an overview of systematic reviews and panoramic meta-analysis. Health Technol Assess 2021;25(9):1-378.
[163] Framework IC. The MOS 36-item short-form health survey (SF-36). Med Care 1992;30(6):473-483.
[164] Frazier JA, Chiu S, Breeze JL, Makris N, Lange N, Kennedy DN, Herbert MR, Bent EK, Koneru VK, Dieterich ME, Hodge SM, Rauch SL, Grant PE, Cohen BM, Seidman LJ, Caviness VS, Biederman J. Structural brain magnetic resonance imaging of limbic and thalamic volumes in pediatric bipolar disorder. Am J Psychiatry 2005;162(7):1256-1265.
[165] Freeman D, Sheaves B, Goodwin GM, Yu LM, Nickless A, Harrison PJ, Emsley R, Luik AI, Foster RG, Wadekar V, Hinds C, Gumley A, Jones R, Lightman S, Jones S, Bentall R, Kinderman P, Rowse G, Brugha T, Blagrove M, Gregory AM, Fleming L, Walklet E, Glazebrook C, Davies EB, Hollis C, Haddock G, John B, Coulson M, Fowler D, Pugh K, Cape J, Moseley P, Brown G, Hughes C, Obonsawin M, Coker S, Watkins E, Schwannauer M, MacMahon K, Siriwardena AN, Espie CA. The effects of improving sleep on mental health (OASIS): a randomised controlled trial with mediation analysis. Lancet Psychiatry 2017;4(10):749-758.
[166] Freynhagen R, Baron R, Gockel U, Tolle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin 2006;22(10):1911-1920.
[167] Galvez-Sánchez CM, de la Coba P, Colmenero JM, Reyes Del Paso GA, Duschek S. Attentional function in fibromyalgia and rheumatoid arthritis. PLoS One 2021;16(1):e0246128.
[168] Galvez-Sanchez CM, Munoz Ladron de Guevara C, Montoro CI, Fernandez-Serrano MJ, Duschek S, Reyes Del Paso GA. Cognitive deficits in fibromyalgia syndrome are associated with pain responses to low intensity pressure stimulation. PLoS One 2018;13(8):e0201488.

[169] Gendreau RM, Thorn MD, Gendreau JF, Kranzler JD, Ribeiro S, Gracely RH, Williams DA, Mease PJ, McLean SA, Clauw DJ. Efficacy of milnacipran in patients with fibromyalgia. J Rheumatol 2005;32(10):1975-1985.
[170] Ghaferi AA, Schwartz TA, Pawlik TM. STROBE reporting guidelines for observational studies. JAMA surgery 2021;156(6):577-578.
[171] Gilbert SJ, Burgess PW. Executive function. Current Biology 2008;18(3):R110-R114.
[172] Gilron I, Chaparro LE, Tu D, Holden RR, Milev R, Towheed T, DuMerton-Shore D, Walker S. Combination of pregabalin with duloxetine for fibromyalgia: a randomized controlled trial. Pain 2016;157(7):1532-1540.
[173] Ginsberg F, Mancaux A, Joos E, Vanhove P, Famaey J-P. A Randomized Placebo-Controlled Trial of Sustained-Release Amitriptyline in Primary Fibromyalgia. Journal of Musculoskeletal Pain 1996;4(3):37-47.
[174] Giordano N, Geraci S, Santacroce C, Mattii G, Battisti E, Gennari C. Efficacy and tolerability of paroxetine in patients with fibromyalgia syndrome: a single-blind study. Current Therapeutic Research 1999;60(12):696-702.
[175] Glass JM, Lyden AK, Petzke F, Stein P, Whalen G, Ambrose K, Chrousos G, Clauw DJ. The effect of brief exercise cessation on pain, fatigue, and mood symptom development in healthy, fit individuals. Journal of psychosomatic research 2004;57(4):391-398.
[176] Glass JM, Park DC. Cognitive dysfunction in fibromyalgia. Curr Rheumatol Rep 2001;3(2):123-127.
[177] Gobin CM, Banks JB, Fins AI, Tartar JL. Poor sleep quality is associated with a negative cognitive bias and decreased sustained attention. Journal of sleep research 2015;24(5):535-542.
[178] Goldenberg D, Mayskiy M, Mossey C, Ruthazer R, Schmid C. A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. Arthritis Rheum 1996;39(11):1852-1859.
[179] Goldenberg DL, Felson DT, Dinerman H. A randomized, controlled trial of amitriptyline and naproxen in the treatment of patients with fibromyalgia. Arthritis Rheum 1986;29(11):1371-1377.
[180] Goldstein JM, Seidman LJ, Makris N, Ahern T, O'Brien LM, Caviness VS, Jr., Kennedy DN, Faraone SV, Tsuang MT. Hypothalamic abnormalities in schizophrenia: sex effects and genetic vulnerability. Biol Psychiatry 2007;61(8):935-945.
[181] Greve DN, Fischl B. Accurate and robust brain image alignment using boundary-based registration. Neuroimage 2009;48(1):63-72.
[182] Griffanti L, Douaud G, Bijsterbosch J, Evangelisti S, Alfaro-Almagro F, Glasser MF, Duff EP, Fitzgibbon S, Westphal R, Carone D, Beckmann CF, Smith SM. Hand classification of fMRI ICA noise components. Neuroimage 2017;154:188-205.
[183] Griffanti L, Salimi-Khorshidi G, Beckmann CF, Auerbach EJ, Douaud G, Sexton CE, Zsoldos E, Ebmeier KP, Filippini N, Mackay CE, Moeller S, Xu J, Yacoub E, Baselli G, Ugurbil K, Miller KL, Smith SM. ICA-based artefact removal and accelerated fMRI acquisition for improved resting state network imaging. Neuroimage 2014;95:232-247.
[184] Grisart JM, Van der Linden M. Conscious and automatic uses of memory in chronic pain patients. Pain 2001;94(3):305-313.
[185] Gudivada V, Apon A, Ding J. Data quality considerations for big data and machine learning: Going beyond data cleaning and transformations. International Journal on Advances in Software 2017;10(1):1-20.
[186] Gulati M, Dursun E, Vincent K, Watt FE. The influence of sex hormones on musculoskeletal pain and osteoarthritis. The Lancet Rheumatology 2023;5(4):e225-e238.
[187] Guo X, Hou C, Tang P, Li R. Chronic Pain, Analgesics, and Cognitive Status: A Comprehensive Mendelian Randomization Study. Anesthesia and analgesia 2023;137(4):896-905.
[188] Hadjipavlou G, Dunckley P, Behrens TE, Tracey I. Determining anatomical connectivities between cortical and brainstem pain processing regions in humans: a diffusion tensor imaging study in healthy controls. Pain 2006;123(1-2):169-178.
[189] Hannonen P, Malminiemi K, Yli-Kerttula U, Isomeri R, Roponen P. A randomized, double-blind, placebo-controlled study of moclobemide and amitriptyline in the treatment of fibromyalgia in females without psychiatric disorder. Br J Rheumatol 1998;37(12):1279-1286.
[190] Harper DE, Ichesco E, Schrepf A, Hampson JP, Clauw DJ, Schmidt-Wilcke T, Harris RE, Harte SE. Resting Functional Connectivity of the Periaqueductal Gray Is Associated With Normal Inhibition and Pathological Facilitation in Conditioned Pain Modulation. J Pain 2018;19(6):635.e631-635.e615.
[191] Harris RE, Clauw DJ, Scott DJ, McLean SA, Gracely RH, Zubieta J-K. Decreased Central μ-Opioid Receptor Availability in Fibromyalgia. The Journal of Neuroscience 2007;27(37):10000-10006.
[192] Harris RE, Napadow V, Huggins JP, Pauer L, Kim J, Hampson J, Sundgren PC, Foerster B, Petrou M, Schmidt-Wilcke T, Clauw DJ. Pregabalin rectifies aberrant brain chemistry, connectivity, and functional response in chronic pain patients. Anesthesiology 2013;119(6):1453-1464.
[193] Harris RE, Sundgren PC, Craig AD, Kirshenbaum E, Sen A, Napadow V, Clauw DJ. Elevated insular glutamate in fibromyalgia is associated with experimental pain. Arthritis Rheum 2009;60(10):3146-3152.
[194] Hassett AL, Marshall E, Bailey AM, Moser S, Clauw DJ, Hooten WM, Urquhart A, Brummett CM. Changes in Anxiety and Depression Are Mediated by Changes in Pain Severity in Patients Undergoing Lower-Extremity Total Joint Arthroplasty. Reg Anesth Pain Med 2018;43(1):14-18.
[195] Häuser W, Walitt B, Fitzcharles M-A, Sommer C. Review of pharmacological therapies in fibromyalgia syndrome. Arthritis Research & Therapy 2014;16(1):201.
[196] Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care & Research 2011;63(S11):S240-S252.
[197] Heinricher MM, Tavares I, Leith JL, Lumb BM. Descending control of nociception: Specificity, recruitment and plasticity. Brain Res Rev 2009;60(1):214-225.
[198] Hermundstad AM, Bassett DS, Brown KS, Aminoff EM, Clewett D, Freeman S, Frithsen A, Johnson A, Tipper CM, Miller MB, Grafton ST, Carlson JM. Structural foundations of resting-state and task-based functional connectivity in the human brain. Proc Natl Acad Sci U S A 2013;110(15):6169-6174.
[199] Hill AB. THE ENVIRONMENT AND DISEASE: ASSOCIATION OR CAUSATION? Proc R Soc Med 1965;58(5):295-300.
[200] Hindmarch I, Dawson J, Stanley N. A Double-Blind Study in Healthy Volunteers to Assess the Effects on Sleep of Pregabalin Compared with Alprazolam and Placebo. Sleep 2005;28(2):187-194.
[201] Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O, DonCarlos L, Hazen N, Herman J, Adams Hillard PJ, Katz ES, Kheirandish-Gozal L, Neubauer DN, O'Donnell AE, Ohayon M, Peever J, Rawding R, Sachdeva RC, Setters B, Vitiello MV, Ware JC. National Sleep Foundation's updated sleep duration recommendations: final report. Sleep Health 2015;1(4):233-243.

[202] Hochman JR, Davis AM, Elkayam J, Gagliese L, Hawker GA. Neuropathic pain symptoms on the modified painDETECT correlate with signs of central sensitization in knee osteoarthritis. Osteoarthritis Cartilage 2013;21(9):1236-1242.
[203] Honda H, Ashizawa R, Kameyama Y, Yoshimoto Y. Chronic pain in older adults with disabilities is associated with cognitive impairment-a prospective cohort study. Psychogeriatrics : the official journal of the Japanese Psychogeriatric Society 2025;25(1):e13210.
[204] Honda H, Ashizawa R, Kameyama Y, Yoshimoto Y. Chronic pain in older adults with disabilities is associated with cognitive impairment-a prospective cohort study. Psychogeriatrics:The Official Journal of the Japanese Psychogeriatric Society 2025;25(1):e13210.
[205] Honey CJ, Sporns O, Cammoun L, Gigandet X, Thiran JP, Meuli R, Hagmann P. Predicting human resting-state functional connectivity from structural connectivity. Proc Natl Acad Sci U S A 2009;106(6):2035-2040.
[206] Hotelling H. Relations between two sets of variates. Breakthroughs in statistics: methodology and distribution: Springer, 1992. pp. 162-190.
[207] Hsieh JC, Ståhle-Bäckdahl M, Hägermark Ö, Stone-Elander S, Rosenquist G, Ingvar M. Traumatic nociceptive pain activates the hypothalamus and the periaqueductal gray: a positron emission tomography study. Pain 1996;64(2):303-314.
[208] Huai X, Jiao Y, Gu X, Zhu H, Chen L, Fan Y, Yu W, Su D, Xie H. Preoperative Chronic Pain as a Risk Factor for Early Postoperative Cognitive Dysfunction in Elderly Patients Undergoing Hip Joint Replacement Surgery: A Prospective Observational Cohort Study. Frontiers in Neuroscience 2021;15:747362.
[209] Huang Z, Liang P, Jia X, Zhan S, Li N, Ding Y, Lu J, Wang Y, Li K. Abnormal amygdala connectivity in patients with primary insomnia: evidence from resting state fMRI. European journal of radiology 2012;81(6):1288-1295.
[210] Ichesco E, Schmidt-Wilcke T, Bhavsar R, Clauw DJ, Peltier SJ, Kim J, Napadow V, Hampson JP, Kairys AE, Williams DA, Harris RE. Altered resting state connectivity of the insular cortex in individuals with fibromyalgia. J Pain 2014;15(8):815-826.e811.
[211] Innes KE, Sambamoorthi U. The Association of Perceived Memory Loss with Osteoarthritis and Related Joint Pain in a Large Appalachian Population. Pain Med 2018;19(7):1340-1356.
[212] Innes KE, Sambamoorthi U. The Association of Osteoarthritis and Related Pain Burden to Incident Alzheimer's Disease and Related Dementias: A Retrospective Cohort Study of U.S. Medicare Beneficiaries. J Alzheimers Dis 2020;75(3):789-805.
[213] IntHout J, Ioannidis JPA, Rovers MM, Goeman JJ. Plea for routinely presenting prediction intervals in meta-analysis. BMJ Open 2016;6(7):e010247.
[214] Iverson GL, Lam RW. Rapid screening for perceived cognitive impairment in major depressive disorder. Ann Clin Psychiatry 2013;25(2):135-140.
[215] Jacobsen HB, Stiles TC, Stubhaug A, Landrø NI, Hansson P. Comparing objective cognitive impairments in patients with peripheral neuropathic pain or fibromyalgia. Scientific Reports 2021;11(1):673.
[216] Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials – a practical guide with flowcharts. BMC Medical Research Methodology 2017;17(1):162.
[217] Janda AM, As-Sanie S, Rajala B, Tsodikov A, Moser SE, Clauw DJ, Brummett CM. Fibromyalgia survey criteria are associated with increased postoperative opioid consumption in women undergoing hysterectomy. Anesthesiology 2015;122(5):1103-1111.
[218] Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 2002;17(2):825-841.
[219] Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM. FSL. Neuroimage 2012;62(2):782-790.
[220] Jensen KB, Kosek E, Petzke F, Carville S, Fransson P, Marcus H, Williams SC, Choy E, Giesecke T, Mainguy Y, Gracely R, Ingvar M. Evidence of dysfunctional pain inhibition in Fibromyalgia reflected in rACC during provoked pain. Pain 2009;144(1-2):95-100.
[221] Jensen KB, Loitoile R, Kosek E, Petzke F, Carville S, Fransson P, Marcus H, Williams SC, Choy E, Mainguy Y, Vitton O, Gracely RH, Gollub R, Ingvar M, Kong J. Patients with fibromyalgia display less functional connectivity in the brain's pain inhibitory network. Mol Pain 2012;8:32.
[222] Jiang L, D'Souza RS, Oh T, Vincent A, Mohabbat AB, Ashmore Z, Mauck WD, Ge L, Whipple MO, McAllister SJ, Wang Z, Qu W. Sex-Related Differences in Symptoms and Psychosocial Outcomes in Patients With Fibromyalgia: A Prospective Questionnaire Study. Mayo Clinic Proceedings: Innovations, Quality and Outcomes 2020;4(6):767-774.
[223] Johnston KJA, Adams MJ, Nicholl BI, Ward J, Strawbridge RJ, Ferguson A, McIntosh AM, Bailey MES, Smith DJ. Genome-wide association study of multisite chronic pain in UK Biobank. PLOS Genetics 2019;15(6):e1008164.
[224] Julious SA. Sample size of 12 per group rule of thumb for a pilot study. Pharmaceutical Statistics 2005;4(4):287-291.
[225] Junco B, Samano Martin Del Campo D, Karakeshishyan V, Bass D, Sobczak E, Swafford E, Bolanos A, Rooks J, Baumel BS, Ramos AR. Long-term brain fog and cognitive impairment in previously hospitalized COVID-19 patients. PloS one 2024;19(8):e0309102.
[226] Jung CM, Ronda JM, Czeisler CA, Wright Jr KP. Comparison of sustained attention assessed by auditory and visual psychomotor vigilance tasks prior to and during sleep deprivation. Journal of sleep research 2011;20(2):348-355.
[227] KA Co, Moldofsky H. Sleep, daytime symptoms, and cognitive performance in patients with fibromyalgia. J Rheumatol 1997;24(10):2014-2023.
[228] Kang D-W, Kim D, Chang L-H, Kim Y-H, Takahashi E, Cain MS, Watanabe T, Sasaki Y. Structural and Functional Connectivity Changes Beyond Visual Cortex in a Later Phase of Visual Perceptual Learning. Scientific Reports 2018;8(1):5186.
[229] Kang Y, Trewern L, Jackman J, McCartney D, Soni A. Chronic pain: definitions and diagnosis. BMJ 2023;381:e076036.
[230] Kaplan CM, Kelleher E, Irani A, Schrepf A, Clauw DJ, Harte SE. Deciphering nociplastic pain: clinical features, risk factors and potential mechanisms. Nat Rev Neurol 2024;20(6):347-363.
[231] Kaplan CM, Schrepf A, Boehnke KF, He Y, Smith T, Williams DA, Bergmans R, Voepel-Lewis T, Hassett AL, Harris RE, Clauw DJ, Beltz AM, Harte SE. Risk Factors for the Development of Multisite Pain in Children. Clin J Pain 2023.
[232] Katz RS, Heard AR, Mills M, Leavitt F. The Prevalence and Clinical Impact of Reported Cognitive Difficulties (Fibrofog) in Patients with Rheumatic Disease with and Without Fibromyalgia. Journal of Clinical Rheumatology 2004;10(2):53-58.
[233] Kempenaers C, Simenon G, Vander Elst M, Fransolet L, Mingard P, de Maertelaer V, Appelboom T, Mendlewicz J. Effect of an antidiencephalon immune serum on pain and sleep in primary fibromyalgia. Neuropsychobiology 1994;30(2-3):66-72.
[234] Kendall SE, Sjøgren P, Pimenta CAM, Højsted J, Kurita GP. The cognitive effects of opioids in chronic non-cancer pain. Pain 2010;150(2):225-230.
[235] Kennedy N, Nelson S, Jerome RN, Edwards TL, Stroud M, Wilkins CH, Harris PA. Recruitment and retention for chronic pain clinical trials: a narrative review. PAIN Reports 2022;7(4):e1007.

[236] Kiger ME, Varpio L. Thematic analysis of qualitative data: AMEE Guide No. 131. Medical Teacher 2020;42(8):846-854.
[237] Killgore WD. Self-reported sleep correlates with prefrontal-amygdala functional connectivity and emotional functioning. Sleep 2013;36(11):1597-1608.
[238] Kim DJ, Lim M, Kim JS, Chung CK. Structural and functional thalamocortical connectivity study in female fibromyalgia. Scientific Reports 2021;11(1):23323.
[239] Kim SY, Flory J, Relton C. Ethics and practice of Trials within Cohorts: An emerging pragmatic trial design. Clinical Trials 2018;15(1):9-16.
[240] Kim YA, Cho YJ, Kwak SG, Ko HJ. Pain and cognitive function in Korean older adults aged 60 years or more: A retrospective longitudinal study. Medicine 2024;103(40):e39952.
[241] Kirova A-M, Bays RB, Lagalwar S. Working Memory and Executive Function Decline across Normal Aging, Mild Cognitive Impairment, and Alzheimer's Disease. BioMed Research International 2015;2015(1):748212.
[242] Kohavi R. A study of cross-validation and bootstrap for accuracy estimation and model selection. Proceedings of the 14th international joint conference on Artificial intelligence - Volume 2. Montreal, Quebec, Canada: Morgan Kaufmann Publishers Inc., 1995. pp. 1137–1143.
[243] Kong J, Tu PC, Zyloney C, Su TP. Intrinsic functional connectivity of the periaqueductal gray, a resting fMRI study. Behav Brain Res 2010;211(2):215-219.
[244] Koroschetz J, Rehm SE, Gockel U, Brosz M, Freynhagen R, Tölle TR, Baron R. Fibromyalgia and neuropathic pain - differences and similarities. A comparison of 3057 patients with diabetic painful neuropathy and fibromyalgia. BMC Neurology 2011;11(1):55.
[245] Kratz AL, Whibley D, Kim S, Sliwinski M, Clauw D, Williams DA. Fibrofog in Daily Life: An Examination of Ambulatory Subjective and Objective Cognitive Function in Fibromyalgia. Arthritis Care Res (Hoboken) 2020;72(12):1669-1677.
[246] Krause AJ, Prather AA, Wager TD, Lindquist MA, Walker MP. The Pain of Sleep Loss: A Brain Characterization in Humans. J Neurosci 2019;39(12):2291-2300.
[247] Kravitz HM, Katz RS. Fibrofog and fibromyalgia: a narrative review and implications for clinical practice. Rheumatology international 2015;35(7):1115-1125.
[248] Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. Journal of general internal medicine 2001;16(9):606-613.
[249] Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989;46(10):1121-1123.
[250] Kushida CA, Chang A, Gadkary C, Guilleminault C, Carrillo O, Dement WC. Comparison of actigraphic, polysomnographic, and subjective assessment of sleep parameters in sleep-disordered patients. Sleep Medicine 2001;2(5):389-396.
[251] Kuznetsova A, Brockhoff PB, Christensen RHB. lmerTest Package: Tests in Linear Mixed Effects Models. Journal of Statistical Software 2017;82(13):1 - 26.
[252] Kyle SD, Aquino MRJ, Miller CB, Henry AL, Crawford MR, Espie CA, Spielman AJ. Towards standardisation and improved understanding of sleep restriction therapy for insomnia disorder: A systematic examination of CBT-I trial content. Sleep Medicine Reviews 2015;23:83-88.
[253] Kyle SD, Hurry ME, Emsley R, Marsden A, Omlin X, Juss A, Spiegelhalder K, Bisdounis L, Luik AI, Espie CA. The effects of digital cognitive behavioral therapy for insomnia on cognitive function: a randomized controlled trial. Sleep 2020;43(9):1-12.
[254] Kyle SD, Morgan K, Espie CA. THE DAYTIME FUNCTIONING AND SLEEP ATTRIBUTION SCALE (DFSAS): A NEW INSOMNIA-SPECIFIC MEASURE TO PROBE DAYTIME IMPAIRMENT AND POOR SLEEP ATTRIBUTIONS. Sleep 2010;33:A192-A193.
[255] Lacasse A, Ware MA, Bourgault P, Lanctôt H, Dorais M, Boulanger A, Cloutier C, Shir Y, Choinière M. Accuracy of Self-reported Prescribed Analgesic Medication Use: Linkage Between the Quebec Pain Registry and the Quebec Administrative Prescription Claims Databases. The Clinical Journal of Pain 2016;32(2):95-102.
[256] Lami MJ, Martínez MP, Miró E, Sanchez AI, Prados G, Caliz R, Vlaeyen JW. Efficacy of combined cognitive-behavioral therapy for insomnia and pain in patients with fibromyalgia: a randomized controlled trial. Cognitive Therapy and Research 2018;42:63-79.
[257] Langner R, Eickhoff SB. Sustaining attention to simple tasks: a meta-analytic review of the neural mechanisms of vigilant attention. Psychol Bull 2013;139(4):870-900.
[258] Lape EC, Selzer F, Collins JE, Losina E, Katz JN. Stability of Measures of Pain Catastrophizing and Widespread Pain Following Total Knee Replacement. Arthritis Care Res (Hoboken) 2020;72(8):1096-1103.
[259] Lau BK, Vaughan CW. Descending modulation of pain: the GABA disinhibition hypothesis of analgesia. Curr Opin Neurobiol 2014;29:159-164.
[260] Leavitt F, Katz RS, Mills M, Heard AR. Cognitive and dissociative manifestations in fibromyalgia. J Clin Rheumatol 2002;8(2):77-84.
[261] Lee DM, Pendleton N, Tajar A, O'Neill TW, O'Connor DB, Bartfai G, Boonen S, Casanueva FF, Finn JD, Forti G, Giwercman A, Han TS, Huhtaniemi IT, Kula K, Lean MEJ, Punab M, Silman AJ, Vanderschueren D, Moseley CM, Wu FCW, McBeth J, Group ES. Chronic widespread pain is associated with slower cognitive processing speed in middle-aged and older European men. Pain 2010;151(1):30-36.
[262] Lee J, Andronesi OC, Torrado-Carvajal A, Ratai EM, Loggia ML, Weerasekera A, Berry MP, Ellingsen DM, Isaro L, Lazaridou A, Paschali M, Grahl A, Wasan AD, Edwards RR, Napadow V. 3D magnetic resonance spectroscopic imaging reveals links between brain metabolites and multidimensional pain features in fibromyalgia. Eur J Pain 2021;25(9):2050-2064.
[263] Leknes S, Brooks JC, Wiech K, Tracey I. Pain relief as an opponent process: a psychophysical investigation. European journal of neuroscience 2008;28(4):794-801.
[264] Lentz MJ, Landis CA, Rothermel J, Shaver JL. Effects of selective slow wave sleep disruption on musculoskeletal pain and fatigue in middle aged women. J Rheumatol 1999;26(7):1586-1592.
[265] Lerman SF, Rudich Z, Brill S, Shalev H, Shahar G. Longitudinal Associations Between Depression, Anxiety, Pain, and Pain-Related Disability in Chronic Pain Patients. Psychosomatic Medicine 2015;77(3):333-341.
[266] Lier EJ, Rijn CMv, Vries Md, Goor Hv, Oosterman JM. The interaction between pain and cognition: on the roles of task complexity and pain intensity. Scandinavian Journal of Pain 2022;22(2):385-395.
[267] Lin RL, Douaud G, Filippini N, Okell TW, Stagg CJ, Tracey I. Structural Connectivity Variances Underlie Functional and Behavioral Changes During Pain Relief Induced by Neuromodulation. Scientific Reports 2017;7(1):41603.
[268] Linnman C, Beucke J-C, Jensen KB, Gollub RL, Kong J. Sex similarities and differences in pain-related periaqueductal gray connectivity. PAIN 2012;153(2):444-454.

[269] Little RJ, D'Agostino R, Cohen ML, Dickersin K, Emerson SS, Farrar JT, Frangakis C, Hogan JW, Molenberghs G, Murphy SA, Neaton JD, Rotnitzky A, Scharfstein D, Shih WJ, Siegel JP, Stern H. The Prevention and Treatment of Missing Data in Clinical Trials. New England Journal of Medicine 2012;367(14):1355-1360.
[270] Little TD. Longitudinal structural equation modeling. New York: The Guilford Press, 2013.
[271] Little TD, Card NA, Bovaird JA, Preacher KJ, Crandall CS. Structural equation modeling of mediation and moderation with contextual factors. Modeling contextual effects in longitudinal studies 2007;1:207-230.
[272] Littlejohn G. Neurogenic neuroinflammation in fibromyalgia and complex regional pain syndrome. Nature Reviews Rheumatology 2015;11(11):639-648.
[273] Littlejohns TJ, Holliday J, Gibson LM, Garratt S, Oesingmann N, Alfaro-Almagro F, Bell JD, Boultwood C, Collins R, Conroy MC, Crabtree N, Doherty N, Frangi AF, Harvey NC, Leeson P, Miller KL, Neubauer S, Petersen SE, Sellors J, Sheard S, Smith SM, Sudlow CLM, Matthews PM, Allen NE. The UK Biobank imaging enhancement of 100,000 participants: rationale, data collection, management and future directions. Nature Communications 2020;11(1):2624.
[274] Liu Z-Q, Vázquez-Rodríguez B, Spreng RN, Bernhardt BC, Betzel RF, Misic B. Time-resolved structure-function coupling in brain networks. Communications Biology 2022;5(1):532.
[275] Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, Ballard C, Banerjee S, Burns A, Cohen-Mansfield J, Cooper C, Fox N, Gitlin LN, Howard R, Kales HC, Larson EB, Ritchie K, Rockwood K, Sampson EL, Samus Q, Schneider LS, Selbæk G, Teri L, Mukadam N. Dementia prevention, intervention, and care. The Lancet 2017;390(10113):2673-2734.
[276] Loggia ML. "Neuroinflammation": does it have a role in chronic pain? Evidence from human imaging. Pain 2024;165(11S):S58-S67.
[277] Loggia ML, Kim J, Gollub RL, Vangel MG, Kirsch I, Kong J, Wasan AD, Napadow V. Default mode network connectivity encodes clinical pain: an arterial spin labeling study. PAIN® 2013;154(1):24-33.
[278] López-Solà M, Woo CW, Pujol J, Deus J, Harrison BJ, Monfort J, Wager TD. Towards a neurophysiological signature for fibromyalgia. Pain 2017;158(1):34-47.
[279] Luettich A, Sievers C, Alfaro Almagro F, Allen M, Jbabdi S, Smith SM, Pattinson KTS. Functional connectivity between interoceptive brain regions is associated with distinct health-related domains: A population-based neuroimaging study. Hum Brain Mapp 2023;44(8):3210-3221.
[280] Lyall DM, Cullen B, Allerhand M, Smith DJ, Mackay D, Evans J, Anderson J, Fawns-Ritchie C, McIntosh AM, Deary IJ, Pell JP. Cognitive Test Scores in UK Biobank: Data Reduction in 480,416 Participants and Longitudinal Stability in 20,346 Participants. PLOS ONE 2016;11(4):e0154222.
[281] Ma Y, Liang L, Zheng F, Shi L, Zhong B, Xie W. Association between sleep duration and cognitive decline. JAMA network open 2020;3(9):e2013573-e2013573.
[282] MacDonald SW, Li SC, Bäckman L. Neural underpinnings of within-person variability in cognitive functioning. Psychol Aging 2009;24(4):792-808.
[283] Macfarlane GJ, Kronisch C, Dean LE, Atzeni F, Häuser W, Fluß E, Choy E, Kosek E, Amris K, Branco J. EULAR revised recommendations for the management of fibromyalgia. Annals of the rheumatic diseases 2017;76(2):318-328.
[284] Macfarlane GJ, Norrie G, Atherton K, Power C, Jones GT. The influence of socioeconomic status on the reporting of regional and widespread musculoskeletal pain: results from the 1958 British Birth Cohort Study. Ann Rheum Dis 2009;68(10):1591-1595.
[285] Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro Scale for Rating Quality of Randomized Controlled Trials. Physical Therapy 2003;83(8):713-721.
[286] Maixner W, Fillingim RB, Williams DA, Smith SB, Slade GD. Overlapping Chronic Pain Conditions: Implications for Diagnosis and Classification. J Pain 2016;17(9 Suppl):T93-T107.
[287] Makris N, Goldstein JM, Kennedy D, Hodge SM, Caviness VS, Faraone SV, Tsuang MT, Seidman LJ. Decreased volume of left and total anterior insular lobule in schizophrenia. Schizophr Res 2006;83(2-3):155-171.
[288] Mansfield KE, Sim J, Jordan JL, Jordan KP. A systematic review and meta-analysis of the prevalence of chronic widespread pain in the general population. Pain 2016;157(1):55-64.
[289] Mansour AR, Baliki MN, Huang L, Torbey S, Herrmann KM, Schnitzer TJ, Apkarian VA. Brain white matter structural properties predict transition to chronic pain. Pain 2013;154(10):2160-2168.
[290] Martella D, Casagrande M, Lupiáñez J. Alerting, orienting and executive control: the effects of sleep deprivation on attentional networks. Experimental brain research 2011;210:81-89.
[291] Martínez MP, Miró E, Sánchez AI, Díaz-Piedra C, Cáliz R, Vlaeyen JW, Buela-Casal G. Cognitive-behavioral therapy for insomnia and sleep hygiene in fibromyalgia: a randomized controlled trial. Journal of behavioral medicine 2014;37(4):683-697.
[292] Martins IP, Maruta C, Alves PN, Loureiro C, Morgado J, Tavares J, Gil-Gouveia R. Cognitive aging in migraine sufferers is associated with more subjective complaints but similar age-related decline: a 5-year longitudinal study. J Headache Pain 2020;21(1):31.
[293] Matthews KA, Patel SR, Pantesco EJ, Buysse DJ, Kamarck TW, Lee L, Hall MH. Similarities and differences in estimates of sleep duration by polysomnography, actigraphy, diary, and self-reported habitual sleep in a community sample. Sleep Health 2018;4(1):96-103.
[294] Maurer LF, Schneider J, Miller CB, Espie CA, Kyle SD. The clinical effects of sleep restriction therapy for insomnia: A meta-analysis of randomised controlled trials. Sleep Medicine Reviews 2021;58:101493.
[295] Mayer TG, Neblett R, Cohen H, Howard KJ, Choi YH, Williams MJ, Perez Y, Gatchel RJ. The development and psychometric validation of the central sensitization inventory. Pain Practice 2012;12(4):276-285.
[296] McCracken LM, Iverson GL. Predicting complaints of impaired cognitive functioning in patients with chronic pain. Journal of pain and symptom management 2001;21(5):392-396.
[297] McCracken LM, Sato A, Wainwright D, House W, Taylor GJ. A feasibility study of brief group-based acceptance and commitment therapy for chronic pain in general practice: recruitment, attendance, and patient views. Primary Health Care Research & Development 2014;15(3):312-323.
[298] McCracken LM, Vowles KE, Eccleston C. Acceptance of chronic pain: component analysis and a revised assessment method. Pain 2004;107(1-2):159-166.
[299] McCrae CS, Mundt JM, Curtis AF, Craggs JG, O'Shea AM, Staud R, Berry RB, Perlstein WM, Robinson ME. Gray Matter Changes Following Cognitive Behavioral Therapy for Patients With Comorbid Fibromyalgia and Insomnia: A Pilot Study. J Clin Sleep Med 2018;14(9):1595-1603.

[300] McCrae CS, Williams J, Roditi D, Anderson R, Mundt JM, Miller MB, Curtis AF, Waxenberg LB, Staud R, Berry RB. Cognitive behavioral treatments for insomnia and pain in adults with comorbid chronic insomnia and fibromyalgia: clinical outcomes from the SPIN randomized controlled trial. Sleep 2019;42(3):zsy234.
[301] McGrath ER, Espie CA, Power A, Murphy AW, Newell J, Kelly C, Duffy N, Gunning P, Gibson I, Bostock S, O'Donnell MJ. Sleep to Lower Elevated Blood Pressure: A Randomized Controlled Trial (SLEPT). Am J Hypertens 2017;30(3):319-327.
[302] McIntyre RS, Cha DS, Soczynska JK, Woldeyohannes HO, Gallaugher LA, Kudlow P, Alsuwaidan M, Baskaran A. Cognitive deficits and functional outcomes in major depressive disorder: determinants, substrates, and treatment interventions. Depress Anxiety 2013;30(6):515-527.
[303] McWilliams LA, Cox BJ, Enns MW. Mood and anxiety disorders associated with chronic pain: an examination in a nationally representative sample. PAIN 2003;106(1):127-133.
[304] Mease PJ, Clauw DJ, Gendreau RM, Rao SG, Kranzler J, Chen W, Palmer RH. The efficacy and safety of milnacipran for treatment of fibromyalgia. a randomized, double-blind, placebo-controlled trial. The Journal of rheumatology 2009;36(2):398-409.
[305] Mease PJ, Russell IJ, Arnold LM, Florian H, Young JP, Jr., Martin SA, Sharma U. A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. J Rheumatol 2008;35(3):502-514.
[306] Meints SM, Edwards RR. Evaluating psychosocial contributions to chronic pain outcomes. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2018;87:168-182.
[307] Melchior M, Poisbeau P, Gaumond I, Marchand S. Insights into the mechanisms and the emergence of sex-differences in pain. Neuroscience 2016;338:63-80.
[308] Milani SA, Sanchez C, Kuo Y-F, Downer B, Al Snih S, Markides KS, Raji M. Pain and incident cognitive impairment in very old Mexican American adults. Journal of the American Geriatrics Society 2024;72(1):226-235.
[309] Miller KL. Multimodal population brain imaging in the UK Biobank prospective epidemiological study. Nat Neurosci 2016;19.
[310] Miller RP, Kori SH, Todd DD. The Tampa Scale: a measure of kinisophobia. The Clinical journal of pain 1991;7(1):51.
[311] Mills EP, Keay KA, Henderson LA. Brainstem Pain-Modulation Circuitry and Its Plasticity in Neuropathic Pain: Insights From Human Brain Imaging Investigations. Frontiers in Pain Research 2021;2.
[312] Mills SEE, Nicolson KP, Smith BH. Chronic pain: a review of its epidemiology and associated factors in population-based studies. Br J Anaesth 2019;123(2):e273-e283.
[313] Miro E, Lupianez J, Hita E, Martinez MP, Sanchez AI, Buela-Casal G. Attentional deficits in fibromyalgia and its relationships with pain, emotional distress and sleep dysfunction complaints. Psychology & health 2011;26(6):765-780.
[314] Miró E, Lupiáñez J, Martínez MP, Sánchez AI, Díaz-Piedra C, Guzmán MA, Buela-Casal G. Cognitive-behavioral therapy for insomnia improves attentional function in fibromyalgia syndrome: a pilot, randomized controlled trial. J Health Psychol 2011;16(5):770-782.
[315] Mitchell LJ, Bisdounis L, Ballesio A, Omlin X, Kyle SD. The impact of cognitive behavioural therapy for insomnia on objective sleep parameters: A meta-analysis and systematic review. Sleep medicine reviews 2019;47:90-102.
[316] Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. The Lancet 2001;357(9263):1191-1194.
[317] Mohs R, Mease P, Arnold LM, Wang F, Ahl J, Gaynor PJ, Wohlreich MM. The effect of duloxetine treatment on cognition in patients with fibromyalgia. Psychosomatic medicine 2012;74(6):628-634.
[318] Moldofsky H. Nonrestorative sleep and symptoms after a febrile illness in patients with fibrositis and chronic fatigue syndromes. Journal of Rheumatology - Supplement 1989;19:150-153.
[319] Moldofsky H, Harris HW, Archambault WT, Kwong T, Lederman S. Effects of bedtime very low dose cyclobenzaprine on symptoms and sleep physiology in patients with fibromyalgia syndrome: a double-blind randomized placebo-controlled study. J Rheumatol 2011;38(12):2653-2663.
[320] Moldofsky H, Inhaber NH, Guinta DR, Alvarez-Horine SB. Effects of sodium oxybate on sleep physiology and sleep/wake-related symptoms in patients with fibromyalgia syndrome: a double-blind, randomized, placebo-controlled study. J Rheumatol 2010;37(10):2156-2166.
[321] Moldofsky H, Lue FA. The relationship of alpha and delta EEG frequencies to pain and mood in 'fibrositis' patients treated with chlorpromazine and L-tryptophan. Electroencephalogr Clin Neurophysiol 1980;50(1-2):71-80.
[322] Moldofsky H, Lue FA, Eisen J, Keystone E, Gorczynski RM. The relationship of interleukin-1 and immune functions to sleep in humans. Psychosom Med 1986;48(5):309-318.
[323] Moldofsky H, Scarisbrick P. Induction of neurasthenic musculoskeletal pain syndrome by selective sleep stage deprivation. Psychosomatic Medicine 1976;38(1):35-44.
[324] Moldofsky H, Scarisbrick P, England R, Smythe H. Musculosketal Symptoms and Non-REM Sleep Disturbance in Patients with “Fibrositis Syndrome” and Healthy Subjects. Biopsychosocial Science and Medicine 1975;37(4):341-351.
[325] Moore DJ, Eccleston C, Keogh E. Cognitive load selectively influences the interruptive effect of pain on attention. PAIN 2017;158(10):2035-2041.
[326] Moriarty O, McGuire BE, Finn DP. The effect of pain on cognitive function: a review of clinical and preclinical research. Prog Neurobiol 2011;93(3):385-404.
[327] Moriarty O, Ruane N, O'Gorman D, Maharaj CH, Mitchell C, Sarma KM, Finn DP, McGuire BE. Cognitive Impairment in Patients with Chronic Neuropathic or Radicular Pain: An Interaction of Pain and Age. Frontiers in Behavioral Neuroscience 2017;11.
[328] Morin CM. Measuring outcomes in randomized clinical trials of insomnia treatments. Sleep medicine reviews 2003;7(3):263-279.
[329] Mosch B, Hagena V, Herpertz S, Ruttorf M, Diers M. Neural correlates of control over pain in fibromyalgia patients. Neuroimage Clin 2023;37:103355.
[330] Nahman-Averbuch H, Timmers I. Neural mechanisms underlying the conditioned pain modulation response: a narrative review of neuroimaging studies. PAIN 2023;164(1):e25-e46.
[331] Naidich TP, Duvernoy HM, Delman BN, Sorensen AG, Kollias SS, Haacke EM. Duvernoy's Atlas of the Human Brain Stem and Cerebellum. Vienna: Springer Vienna, 2009.
[332] Napadow V, Kim J, Clauw DJ, Harris RE. Decreased intrinsic brain connectivity is associated with reduced clinical pain in fibromyalgia. Arthritis Rheum 2012;64(7):2398-2403.
[333] Napadow V, LaCount L, Park K, As-Sanie S, Clauw DJ, Harris RE. Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. Arthritis Rheum 2010;62(8):2545-2555.
[334] Napadow V, Sclocco R, Henderson LA. Brainstem neuroimaging of nociception and pain circuitries. Pain Rep 2019;4(4):e745.

[335] Naugle KM, Ohlman T, Naugle KE, Riley ZA, Keith NR. Physical activity behavior predicts endogenous pain modulation in older adults. Pain 2017;158(3):383-390.
[336] Nelson SM, Cunningham NR, Kashikar-Zuck S. A conceptual framework for understanding the role of adverse childhood experiences in pediatric chronic pain. The Clinical journal of pain 2017;33(3):264.
[337] Ng AY. Preventing" overfitting" of cross-validation data, Proceedings of the ICML, Vol. 97: Citeseer, 1997. pp. 245-253.
[338] Nørregaard J, Volkmann H, Danneskiold-Samstøe B. A randomized controlled trial of citalopram in the treatment of fibromyalgia. Pain 1995;61(3):445-449.
[339] Oh G, Moga DC, Fardo DW, Abner EL. The association of gabapentin use and change of cognitive and functional status in older adults with normal cognition. Alzheimer's & Dementia 2022;18(S11):e065299.
[340] Ohta H, Oka H, Usui C, Ohkura M, Suzuki M, Nishioka K. A randomized, double-blind, multicenter, placebo-controlled phase III trial to evaluate the efficacy and safety of pregabalin in Japanese patients with fibromyalgia. Arthritis Res Ther 2012;14(5):R217.
[341] Older SA, Battafarano DF, Danning CL, Ward JA, Grady EP, Derman S, Russell IJ. The effects of delta wave sleep interruption on pain thresholds and fibromyalgia-like symptoms in healthy subjects; correlations with insulin-like growth factor I. J Rheumatol 1998;25(6):1180-1186.
[342] Olin R, Klein R, Berg PA. A randomised double-blind 16-week study of ritanserin in fibromyalgia syndrome: clinical outcome and analysis of autoantibodies to serotonin, gangliosides and phospholipids. Clin Rheumatol 1998;17(2):89-94.
[343] Oliva V, Gregory R, Brooks JCW, Pickering AE. Central pain modulatory mechanisms of attentional analgesia are preserved in fibromyalgia. PAIN 2022;163(1):125-136.
[344] Oliva V, Gregory R, Davies W-E, Harrison L, Moran R, Pickering AE, Brooks JCW. Parallel cortical-brainstem pathways to attentional analgesia. NeuroImage 2021;226:117548.
[345] Oliva V, Hartley-Davies R, Moran R, Pickering AE, Brooks JCW. Simultaneous brain, brainstem, and spinal cord pharmacological-fMRI reveals involvement of an endogenous opioid network in attentional analgesia. eLife 2022;11:e71877.
[346] Ong W-Y, Stohler CS, Herr DR. Role of the prefrontal cortex in pain processing. Molecular neurobiology 2019;56(2):1137-1166.
[347] Orsmond GI, Cohn ES. The distinctive features of a feasibility study: Objectives and guiding questions. OTJR: Occupation, Participation and Health 2015;35(3):169-177.
[348] Pala O PD, Reed G, Kremer J. The Impact of Disease Activity on Patient-Reported Cognitive Dysfunction in Rheumatoid Arthritis [abstract]. Arthritis Rheumatology 2022;74.
[349] Pardi D, Black J. γ-Hydroxybutyrate/Sodium Oxybate. CNS Drugs 2006;20(12):993-1018.
[350] Park HS, Park JY, Yu R. Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF-α and IL-6. Diabetes Research and Clinical Practice 2005;69(1):29-35.
[351] Pask S, Dell'Olio M, Murtagh FEM, Boland JW. The Effects of Opioids on Cognition in Older Adults With Cancer and Chronic Noncancer Pain: A Systematic Review. J Pain Symptom Manage 2020;59(4):871-893.e871.
[352] Pauer L, Winkelmann A, Arsenault P, Jespersen A, Whelan L, Atkinson G, Leon T, Zeiher B. An international, randomized, double-blind, placebo-controlled, phase III trial of pregabalin monotherapy in treatment of patients with fibromyalgia. J Rheumatol 2011;38(12):2643-2652.
[353] Peek AL, Rebbeck T, Puts NA, Watson J, Aguila MR, Leaver AM. Brain GABA and glutamate levels across pain conditions: A systematic literature review and meta-analysis of 1H-MRS studies using the MRS-Q quality assessment tool. Neuroimage 2020;210:116532.
[354] Pickering G, Jourdan D, Eschalier A, Dubray C. Impact of age, gender and cognitive functioning on pain perception. Gerontology 2002;48(2):112-118.
[355] Pickering G, Pereira B, Clere F, Sorel M, de Montgazon G, Navez M, Picard P, Roux D, Morel V, Salimani R, Adda M, Legout V, Dubray C. Cognitive function in older patients with postherpetic neuralgia. Pain practice : the official journal of World Institute of Pain 2014;14(1):E1-7.
[356] Pinto AM, Geenen R, Wager TD, Lumley MA, Häuser W, Kosek E, Ablin JN, Amris K, Branco J, Buskila D, Castelhano J, Castelo-Branco M, Crofford LJ, Fitzcharles MA, López-Solà M, Luís M, Marques TR, Mease PJ, Palavra F, Rhudy JL, Uddin LQ, Castilho P, Jacobs JWG, da Silva JAP. Emotion regulation and the salience network: a hypothetical integrative model of fibromyalgia. Nat Rev Rheumatol 2022.
[357] Potvin S, Marchand S. Pain facilitation and pain inhibition during conditioned pain modulation in fibromyalgia and in healthy controls. Pain 2016;157(8):1704-1710.
[358] Potvin S, Morin M, Cloutier C, Gendron A, Bissonnette A, Marchand S. Add-on treatment of quetiapine for fibromyalgia: a pilot, randomized, double-blind, placebo-controlled 12-week trial. J Clin Psychopharmacol 2012;32(5):684-687.
[359] Puiu T, Kairys AE, Pauer L, Schmidt-Wilcke T, Ichesco E, Hampson JP, Napadow V, Clauw DJ, Harris RE. Association of Alterations in Gray Matter Volume With Reduced Evoked-Pain Connectivity Following Short-Term Administration of Pregabalin in Patients With Fibromyalgia. Arthritis & Rheumatology 2016;68(6):1511-1521.
[360] Pujol J, Macia D, Garcia-Fontanals A, Blanco-Hinojo L, Lopez-Sola M, Garcia-Blanco S, Poca-Dias V, Harrison BJ, Contreras-Rodriguez O, Monfort J, Garcia-Fructuoso F, Deus J. The contribution of sensory system functional connectivity reduction to clinical pain in fibromyalgia. Pain 2014;155(8):1492-1503.
[361] Pyke TL, Osmotherly PG, Baines S. Measuring Glutamate Levels in the Brains of Fibromyalgia Patients and a Potential Role for Glutamate in the Pathophysiology of Fibromyalgia Symptoms: A Systematic Review. Clin J Pain 2017;33(10):944-954.
[362] Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD. Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med 2016;165(2):125-133.
[363] Quigley M, Cordes D, Turski P, Moritz C, Haughton V, Seth R, Meyerand ME. Role of the corpus callosum in functional connectivity. AJNR Am J Neuroradiol 2003;24(2):208-212.
[364] Rader L, Wager TD, Friedman NP. Chronic pain is specifically associated with updating working memory: a longitudinal twin study. Pain 2025;166(1):212-221.
[365] Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, Keefe FJ, Mogil JS, Ringkamp M, Sluka KA, Song X-J, Stevens B, Sullivan MD, Tutelman PR, Ushida T, Vader K. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. PAIN 2020;Articles in Press.
[366] Rehm SE, Koroschetz J, Gockel U, Brosz M, Freynhagen R, Tölle TR, Baron R. A cross-sectional survey of 3035 patients with fibromyalgia: subgroups of patients with typical comorbidities and sensory symptom profiles. Rheumatology (Oxford) 2010;49(6):1146-1152.

[367] Riemann D, Espie CA, Altena E, Arnardottir ES, Baglioni C, Bassetti CLA, Bastien C, Berzina N, Bjorvatn B, Dikeos D, Dolenc Groselj L, Ellis JG, Garcia-Borreguero D, Geoffroy PA, Gjerstad M, Gonçalves M, Hertenstein E, Hoedlmoser K, Hion T, Holzinger B, Janku K, Jansson-Fröjmark M, Järnefelt H, Jernelöv S, Jennum PJ, Khachatryan S, Krone L, Kyle SD, Lancee J, Leger D, Lupusor A, Marques DR, Nissen C, Palagini L, Paunio T, Perogamvros L, Pevernagie D, Schabus M, Shochat T, Szentkiralyi A, Van Someren E, van Straten A, Wichniak A, Verbraecken J, Spiegelhalder K. The European Insomnia Guideline: An update on the diagnosis and treatment of insomnia 2023. Journal of Sleep Research 2023;32(6):e14035.
[368] Riemann D, Spiegelhalder K, Feige B, Voderholzer U, Berger M, Perlis M, Nissen C. The hyperarousal model of insomnia: a review of the concept and its evidence. Sleep Med Rev 2010;14(1):19-31.
[369] Rifbjerg-Madsen S, Wæhrens EE, Danneskiold-Samsøe B, Amris K. Psychometric properties of the painDETECT questionnaire in rheumatoid arthritis, psoriatic arthritis and spondyloarthritis: Rasch analysis and test-retest reliability. Health Qual Life Outcomes 2017;15(1):110.
[370] Rist PM, Dufouil C, Glymour MM, Tzourio C, Kurth T. Migraine and cognitive decline in the population-based EVA study. Cephalalgia 2011;31(12):1291-1300.
[371] Ritchie CS, Patel K, Boscardin J, Miaskowski C, Vranceanu A-M, Whitlock E, Smith A. Impact of persistent pain on function, cognition, and well-being of older adults. Journal of the American Geriatrics Society 2023;71(1):26-35.
[372] Rizzi M, Sarzi-Puttini P, Atzeni F, Capsoni F, Andreoli A, Pecis M, Colombo S, Carrabba M, Sergi M. Cyclic alternating pattern: a new marker of sleep alteration in patients with fibromyalgia? J Rheumatol 2004;31(6):1193-1199.
[373] Robison MK, Ellis DM, Pitaes MM, Karoly P, Brewer GA. Acute pain impairs sustained attention. J Exp Psychol Appl 2021;27(3):563-577.
[374] Roizenblatt S, Moldofsky H, Benedito-Silva AA, Tufik S. Alpha sleep characteristics in fibromyalgia. Arthritis Rheum 2001;44(1):222-230.
[375] Rolke R, Baron R, Maier C, Tölle TR, Treede DR, Beyer A, Binder A, Birbaumer N, Birklein F, Bötefür IC, Braune S, Flor H, Huge V, Klug R, Landwehrmeyer GB, Magerl W, Maihöfner C, Rolko C, Schaub C, Scherens A, Sprenger T, Valet M, Wasserka B. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. Pain 2006;123(3):231-243.
[376] Rolke R, Magerl W, Campbell KA, Schalber C, Caspari S, Birklein F, Treede RD. Quantitative sensory testing: a comprehensive protocol for clinical trials. Eur J Pain 2006;10(1):77-88.
[377] Rong W, Zhang C, Zheng F, Xiao S, Yang Z, Xie W. Persistent moderate to severe pain and long-term cognitive decline. European Journal of Pain 2021;25(9):2065-2074.
[378] Rosenberg M, Noonan S, DeGutis J, Esterman M. Sustaining visual attention in the face of distraction: a novel gradual-onset continuous performance task. Atten Percept Psychophys 2013;75(3):426-439.
[379] Rosenberg MD, Finn ES, Scheinost D, Papademetris X, Shen X, Constable RT, Chun MM. A neuromarker of sustained attention from whole-brain functional connectivity. Nat Neurosci 2016;19(1):165-171.
[380] Rosenberg MD, Scheinost D, Greene AS, Avery EW, Kwon YH, Finn ES, Ramani R, Qiu M, Constable RT, Chun MM. Functional connectivity predicts changes in attention observed across minutes, days, and months. Proceedings of the National Academy of Sciences 2020;117(7):3797-3807.
[381] Rossini M, Di Munno O, Valentini G, Bianchi G, Biasi G, Cacace E, Malesci D, La Montagna G, Viapiana O, Adami S. Double-blind, multicenter trial comparing acetyl l-carnitine with placebo in the treatment of fibromyalgia patients. Clin Exp Rheumatol 2007;25(2):182-188.
[382] Roth T, Arnold LM, Garcia-Borreguero D, Resnick M, Clair AG. A review of the effects of pregabalin on sleep disturbance across multiple clinical conditions. Sleep Medicine Reviews 2014;18(3):261-271.
[383] Roth T, Lankford DA, Bhadra P, Whalen E, Resnick EM. Effect of pregabalin on sleep in patients with fibromyalgia and sleep maintenance disturbance: a randomized, placebo-controlled, 2-way crossover polysomnography study. Arthritis Care Res (Hoboken) 2012;64(4):597-606.
[384] Rothlein D, DeGutis J, Esterman M. Attentional Fluctuations Influence the Neural Fidelity and Connectivity of Stimulus Representations. Journal of Cognitive Neuroscience 2018;30(9):1209-1228.
[385] Rouch I, Edjolo A, Laurent B, Pongan E, Dartigues JF, Amieva H. Association between chronic pain and long-term cognitive decline in a population-based cohort of elderly participants. Pain 2021;162(2):552-560.
[386] Russell IJ, Crofford LJ, Leon T, Cappelleri JC, Bushmakin AG, Whalen E, Barrett JA, Sadosky A. The effects of pregabalin on sleep disturbance symptoms among individuals with fibromyalgia syndrome. Sleep Medicine 2009;10(6):604-610.
[387] Russell IJ, Perkins AT, Michalek JE. Sodium oxybate relieves pain and improves function in fibromyalgia syndrome: a randomized, double-blind, placebo-controlled, multicenter clinical trial. Arthritis Rheum 2009;60(1):299-309.
[388] Russell JI, Holman AJ, Swick TJ, Alvarez-Horine S, Wang GY, Guinta D. Sodium oxybate reduces pain, fatigue, and sleep disturbance and improves functionality in fibromyalgia: results from a 14-week, randomized, double-blind, placebo-controlled study. Pain 2011;152(5):1007-1017.
[389] Rutkowski L, Svetina D. Assessing the hypothesis of measurement invariance in the context of large-scale international surveys. Educational and psychological measurement 2014;74(1):31-57.
[390] Rutter-Locher Z, Arumalla N, Norton S, Taams LS, Kirkham BW, Bannister K. A systematic review and meta-analysis of questionnaires to screen for pain sensitisation and neuropathic like pain in inflammatory arthritis. Seminars in Arthritis and Rheumatism 2023;61:152207.
[391] Sadlon A, Takousis P, Ankli B, Alexopoulos P, Perneczky R. Association of Chronic Pain with Biomarkers of Neurodegeneration, Microglial Activation, and Inflammation in Cerebrospinal Fluid and Impaired Cognitive Function. Annals of Neurology 2023;03:03.
[392] Sadlon A, Takousis P, Ankli B, Alexopoulos P, Perneczky R, Initiative AsDN. Association of Chronic Pain with Biomarkers of Neurodegeneration, Microglial Activation, and Inflammation in Cerebrospinal Fluid and Impaired Cognitive Function. Annals of neurology 2024;95(1):195-206.
[393] Salazar-Méndez J, Viscay-Sanhueza N, Pinto-Vera C, Oyarce-Contreras F, Parra-Vera M-F, Suso-Martí L, Guzmán-Muñoz E, López-Bueno R, Núñez-Cortés R, Calatayud J. Cognitive behavioral therapy for insomnia in people with chronic musculoskeletal pain. A systematic review and dose-response meta-analysis. Sleep Medicine 2024;122:20-26.
[394] Salimi-Khorshidi G, Douaud G, Beckmann CF, Glasser MF, Griffanti L, Smith SM. Automatic denoising of functional MRI data: combining independent component analysis and hierarchical fusion of classifiers. Neuroimage 2014;90:449-468.

[395] Sánchez AI, Díaz-Piedra C, Miró E, Martínez MP, Gálvez R, Buela-Casal G. Effects of cognitive-behavioral therapy for insomnia on polysomnographic parameters in fibromyalgia patients. International Journal of Clinical and Health Psychology 2012;12(1):39-53.
[396] Santillo AF, Strandberg TO, Reislev NH, Nilsson M, Stomrud E, Spotorno N, van Westen D, Hansson O. Divergent functional connectivity changes associated with white matter hyperintensities. Neuroimage 2024;296:120672.
[397] Saral I, Sindel D, Esmaeilzadeh S, Sertel-Berk HO, Oral A. The effects of long- and short-term interdisciplinary treatment approaches in women with fibromyalgia: a randomized controlled trial. Rheumatol Int 2016;36(10):1379-1389.
[398] Sardi NF, Lazzarim MK, Guilhen VA, Marcílio RS, Natume PS, Watanabe TC, Lima MM, Tobaldini G, Fischer L. Chronic sleep restriction increases pain sensitivity over time in a periaqueductal gray and nucleus accumbens dependent manner. Neuropharmacology 2018;139:52-60.
[399] Sarzi-Puttini P, Giorgi V, Marotto D, Atzeni F. Fibromyalgia: an update on clinical characteristics, aetiopathogenesis and treatment. Nature Reviews Rheumatology 2020;16(11):645-660.
[400] Schmidt AF, Finan C. Linear regression and the normality assumption. Journal of Clinical Epidemiology 2018;98:146-151.
[401] Schrepf A, Moser S, Harte SE, Basu N, Kaplan C, Kolarik E, Tsodikov A, Brummett CM, Clauw DJ. Top down or bottom up? An observational investigation of improvement in fibromyalgia symptoms following hip and knee replacement. Rheumatology 2020;59(3):594-602.
[402] Schrepf A, Williams DA, Gallop R, Naliboff BD, Basu N, Kaplan C, Harper DE, Landis JR, Clemens JQ, Strachan E, Griffith JW, Afari N, Hassett A, Pontari MA, Clauw DJ, Harte SE. Sensory sensitivity and symptom severity represent unique dimensions of chronic pain: a MAPP Research Network study. Pain 2018;159(10):2002-2011.
[403] Schulz KF, Grimes DA. Multiplicity in randomised trials I: endpoints and treatments. The Lancet 2005;365(9470):1591-1595.
[404] Seminowicz DA, Davis KD. Interactions of pain intensity and cognitive load: the brain stays on task. Cereb Cortex 2007;17(6):1412-1422.
[405] Senn S. Testing for baseline balance in clinical trials. Statistics in medicine 1994;13(17):1715-1726.
[406] Seymour B, Crook RJ, Chen ZS. Post-injury pain and behaviour: a control theory perspective. Nature Reviews Neuroscience 2023;24(6):378-392.
[407] Sharp PB, Miller GA, Heller W. Transdiagnostic dimensions of anxiety: Neural mechanisms, executive functions, and new directions. International Journal of Psychophysiology 2015;98(2, Part 2):365-377.
[408] Shega JW, Weiner DK, Paice JA, Bilir SP, Rockwood K, Herr K, Ersek M, Emanuel L, Dale W. The association between noncancer pain, cognitive impairment, and functional disability: an analysis of the Canadian study of health and aging. J Gerontol A Biol Sci Med Sci 2010;65(8):880-886.
[409] Shen X, Finn ES, Scheinost D, Rosenberg MD, Chun MM, Papademetris X, Constable RT. Using connectome-based predictive modeling to predict individual behavior from brain connectivity. Nat Protoc 2017;12(3):506-518.
[410] Shen X, Tokoglu F, Papademetris X, Constable RT. Groupwise whole-brain parcellation from resting-state fMRI data for network node identification. Neuroimage 2013;82:403-415.
[411] Shields GS, Moons WG, Tewell CA, Yonelinas AP. The effect of negative affect on cognition: Anxiety, not anger, impairs executive function. Emotion 2016;16(6):792-797.
[412] Shiers S, Pradhan G, Mwirigi J, Mejia G, Ahmad A, Kroener S, Price T. Neuropathic Pain Creates an Enduring Prefrontal Cortex Dysfunction Corrected by the Type II Diabetic Drug Metformin But Not by Gabapentin. The Journal of Neuroscience 2018;38(33):7337-7350.
[413] Sim J, Lewis M. The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. J Clin Epidemiol 2012;65(3):301-308.
[414] Singer JD, Willett JB. Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence: Oxford University Press, 2003.
[415] Sluka KA, O'Donnell JM, Danielson J, Rasmussen LA. Regular physical activity prevents development of chronic pain and activation of central neurons. J Appl Physiol 2013;114(6):725-733.
[416] Smallwood J, Davies JB, Heim D, Finnigan F, Sudberry M, O'Connor R, Obonsawin M. Subjective experience and the attentional lapse: Task engagement and disengagement during sustained attention. Consciousness and cognition 2004;13(4):657-690.
[417] Smejka T, Henry AL, Wheatley C, Espie CA, Johansen-Berg H, Fleming MK. A qualitative examination of the usability of a digital cognitive behavioral therapy for insomnia program after stroke. Brain Injury 2022;36(2):271-278.
[418] Smith BH, Fors EA, Korwisi B, Barke A, Cameron P, Colvin L, Richardson C, Rief W, Treede RD. The IASP classification of chronic pain for ICD-11: applicability in primary care. Pain 2019;160(1):83-87.
[419] Smith DJ, Nicholl BI, Cullen B, Martin D, Ul-Haq Z, Evans J, Gill JMR, Roberts B, Gallacher J, Mackay D, Hotopf M, Deary I, Craddock N, Pell JP. Prevalence and Characteristics of Probable Major Depression and Bipolar Disorder within UK Biobank: Cross-Sectional Study of 172,751 Participants. PLOS ONE 2013;8(11):e75362.
[420] Smith SM, Alfaro-Almagro F, Miller KL. UK Biobank Brain Imaging Documentation Version 1.10: UK Biobank, 2024.
[421] Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, Filippini N, Watkins KE, Toro R, Laird AR, Beckmann CF. Correspondence of the brain's functional architecture during activation and rest. Proceedings of the National Academy of Sciences 2009;106(31):13040-13045.
[422] Smith SM, Nichols TE, Vidaurre D, Winkler AM, Behrens TE, Glasser MF, Ugurbil K, Barch DM, Van Essen DC, Miller KL. A positive-negative mode of population covariation links brain connectivity, demographics and behavior. Nat Neurosci 2015;18(11):1565-1567.
[423] Snitz BE, Small BJ, Wang T, Chang C-CH, Hughes TF, Ganguli M. Do subjective memory complaints lead or follow objective cognitive change? A five-year population study of temporal influence. Journal of the International Neuropsychological Society 2015;21(9):732-742.
[424] Soh HL, Ho RC, Ho CS, Tam WW. Efficacy of digital cognitive behavioural therapy for insomnia: a meta-analysis of randomised controlled trials. Sleep medicine 2020;75:315-325.
[425] Soni A, Santos-Paulo S, Segerdahl A, Javaid MK, Pinedo-Villanueva R, Tracey I. Hospitalization in fibromyalgia: a cohort-level observational study of in-patient procedures, costs and geographical variation in England. Rheumatology 2020;59(8):2074-2084.
[426] Spaeth M. Is pregabalin a safe and effective treatment for patients with fibromyalgia? [Miscellaneous]. Nature Clinical Practice Rheumatology 2008;4(10):514-515.
[427] Spaeth M. Epidemiology, costs, and the economic burden of fibromyalgia. Arthritis Research & Therapy 2009;11(3):117.
[428] Spaeth M, Bennett RM, Benson BA, Wang YG, Lai C, Choy EH. Sodium oxybate therapy provides multidimensional improvement in fibromyalgia: results of an international phase 3 trial. Ann Rheum Dis 2012;71(6):935-942.

[429] Spisak T, Kincses B, Schlitt F, Zunhammer M, Schmidt-Wilcke T, Kincses ZT, Bingel U. Pain-free resting-state functional brain connectivity predicts individual pain sensitivity. Nature Communications 2020;11(1):187.
[430] Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Archives of internal medicine 2006;166(10):1092-1097.
[431] Stein N, Sprenger C, Scholz J, Wiech K, Bingel U. White matter integrity of the descending pain modulatory system is associated with interindividual differences in placebo analgesia. Pain 2012;153(11):2210-2217.
[432] Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, Wood AM, Carpenter JR. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. Bmj 2009;338:b2393.
[433] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. Bmj 2019;366:l4898.
[434] Stott R, Pimm J, Emsley R, Miller CB, Espie CA. Does adjunctive digital CBT for insomnia improve clinical outcomes in an improving access to psychological therapies service? Behaviour Research and Therapy 2021;144:103922.
[435] Straube S, Derry S, Moore RA, McQuay HJ. Pregabalin in fibromyalgia: meta-analysis of efficacy and safety from company clinical trial reports. Rheumatology 2010;49(4):706-715.
[436] Stubbs B, Binnekade T, Eggermont L, Sepehry AA, Patchay S, Schofield P. Pain and the risk for falls in community-dwelling older adults: systematic review and meta-analysis. Arch Phys Med Rehabil 2014;95(1):175-187.e179.
[437] Stubbs B, Patchay S, Soundy A, Schofield P. The avoidance of activities due to fear of falling contributes to sedentary behavior among community-dwelling older adults with chronic musculoskeletal pain: a multisite observational study. Pain medicine (Malden, Mass) 2014;15(11):1861-1871.
[438] Sullivan MJ, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. Psychological assessment 1995;7(4):524.
[439] Sullivan MJ, Thorn B, Haythornthwaite JA, Keefe F, Martin M, Bradley LA, Lefebvre JC. Theoretical perspectives on the relation between catastrophizing and pain. The Clinical journal of pain 2001;17(1):52-64.
[440] Sunol M, Dudley J, Payne MF, Tong H, Ting TV, Kashikar-Zuck S, Coghill RC, Lopez-Sola M. Reduced Cortico-Cortical Resting-State Connectivity in Sensory Systems is related to Bodily Pain in Juvenile Fibromyalgia. Arthritis Rheumatol 2023.
[441] Swanson JM. The UK Biobank and selection bias. Lancet 2012;380(9837):110.
[442] Tai XY, Chen C, Manohar S, Husain M. Impact of sleep duration on executive function and brain structure. Communications biology 2022;5(1):201.
[443] Tang NK, Lereya ST, Boulton H, Miller MA, Wolke D, Cappuccio FP. Nonpharmacological Treatments of Insomnia for Long-Term Painful Conditions: A Systematic Review and Meta-analysis of Patient-Reported Outcomes in Randomized Controlled Trials. Sleep 2015;38(11):1751-1764.
[444] Tannenbaum C, Paquette A, Hilmer S, Holroyd-Leduc J, Carnahan R. A Systematic Review of Amnestic and Non-Amnestic Mild Cognitive Impairment Induced by Anticholinergic, Antihistamine, GABAergic and Opioid Drugs. Drugs & Aging 2012;29(8):639-658.
[445] Teodoro T, Edwards MJ, Isaacs JD. A unifying theory for cognitive abnormalities in functional neurological disorders, fibromyalgia and chronic fatigue syndrome: systematic review. Journal of Neurology, Neurosurgery & Psychiatry 2018;89(12):1308-1319.
[446] Terassi M, Montoya P, Pavarini SCI, Hortense P. Influence of chronic pain on cognitive performance in elderly caregivers: a longitudinal study. Rev Bras Enferm 2021;74(suppl 2):e20200412.
[447] Terassi M, Montoya P, Pavarini SCI, Hortense P. Influence of chronic pain on cognitive performance in elderly caregivers: a longitudinal study. Revista Brasileira de Enfermagem 2021;74(suppl 2):e20200412.
[448] Tian J, Jones G, Lin X, Zhou Y, King A, Vickers J, Pan F. Association between chronic pain and risk of incident dementia: findings from a prospective cohort. BMC Med 2023;21(1):169.
[449] Tomim DH, Pontarolla FM, Bertolini JF, Arase M, Tobaldini G, Lima MMS, Fischer L. The Pronociceptive Effect of Paradoxical Sleep Deprivation in Rats: Evidence for a Role of Descending Pain Modulation Mechanisms. Molecular Neurobiology 2016;53(3):1706-1717.
[450] Townsend P. Deprivation. Journal of Social Policy 1987;16(2):125-146.
[451] Tracey I, Bushnell MC. How neuroimaging studies have challenged us to rethink: is chronic pain a disease? J Pain 2009;10(11):1113-1120.
[452] Tracey I, Ploghaus A, Gati JS, Clare S, Smith S, Menon RS, Matthews PM. Imaging attentional modulation of pain in the periaqueductal gray in humans. J Neurosci 2002;22(7):2748-2752.
[453] Trauer JM, Qian MY, Doyle JS, Rajaratnam SM, Cunnington D. Cognitive behavioral therapy for chronic insomnia: a systematic review and meta-analysis. Annals of internal medicine 2015;163(3):191-204.
[454] Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB, Giamberardino MA, Kaasa S, Korwisi B, Kosek E, Lavand'homme P, Nicholas M, Perrot S, Scholz J, Schug S, Smith BH, Svensson P, Vlaeyen JWS, Wang SJ. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). Pain 2019;160(1):19-27.
[455] Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB, Giamberardino MA, Kaasa S, Kosek E, Lavand'homme P, Nicholas M, Perrot S, Scholz J, Schug S, Smith BH, Svensson P, Vlaeyen JW, Wang SJ. A classification of chronic pain for ICD-11. Pain 2015;156(6):1003-1007.
[456] Turk-Browne NB. Functional interactions as big data in the human brain. Science 2013;342(6158):580-584.
[457] Twisk JWR. Applied Longitudinal Data Analysis for Epidemiology: A Practical Guide. Cambridge: Cambridge University Press, 2013.
[458] Vaerøy H, Abrahamsen A, Førre O, Kåss E. Treatment of fibromyalgia (fibrositis syndrome): a parallel double blind trial with carisoprodol, paracetamol and caffeine (Somadril comp) versus placebo. Clin Rheumatol 1989;8(2):245-250.
[459] Valet M, Sprenger T, Boecker H, Willoch F, Rummeny E, Conrad B, Erhard P, Tolle TR. Distraction modulates connectivity of the cingulo-frontal cortex and the midbrain during pain—an fMRI analysis. Pain 2004;109(3):399-408.
[460] Valko PO, Bassetti CL, Bloch KE, Held U, Baumann CR. Validation of the fatigue severity scale in a Swiss cohort. Sleep 2008;31(11):1601-1607.
[461] Van Damme S, Becker S, Van der Linden D. Tired of pain? Toward a better understanding of fatigue in chronic pain. PAIN 2018;159(1):7-10.

[462] van der Leeuw G, Ayers E, Leveille SG, Blankenstein AH, van der Horst HE, Verghese J. The Effect of Pain on Major Cognitive Impairment in Older Adults. J Pain 2018;19(12):1435-1444.
[463] van der Leeuw G, Eggermont LHP, Shi L, Milberg WP, Gross AL, Hausdorff JM, Bean JF, Leveille SG. Pain and Cognitive Function Among Older Adults Living in the Community. The journals of gerontology Series A, Biological sciences and medical sciences 2016;71(3):398-405.
[464] van der Leeuw G, Leveille SG, Dong Z, Shi L, Habtemariam D, Milberg W, Hausdorff JM, Grande L, Gagnon P, McLean RR, Bean JF. Chronic Pain and Attention in Older Community-Dwelling Adults. Journal of the American Geriatrics Society 2018;66(7):1318-1324.
[465] Varghese S, Frey BN, Schneider MA, Kapczinski F, de Azevedo Cardoso T. Functional and cognitive impairment in the first episode of depression: A systematic review. Acta Psychiatrica Scandinavica 2022;145(2):156-185.
[466] Veldhuijzen DS, Kenemans JL, de Bruin CM, Olivier B, Volkerts ER. Pain and Attention: Attentional Disruption or Distraction? The Journal of Pain 2006;7(1):11-20.
[467] Veldsman M, Tai X-Y, Nichols T, Smith S, Peixoto J, Manohar S, Husain M. Cerebrovascular risk factors impact frontoparietal network integrity and executive function in healthy ageing. Nature Communications 2020;11(1):4340.
[468] Verhoeven K, Stefaan VD, Christopher E, Van Ryckeghem Dimitri ML, Valéry L, Geert C. Distraction from pain and executive functioning: An experimental investigation of the role of inhibition, task switching and working memory. European Journal of Pain 2011;15(8):866-873.
[469] Vernon MK, Dugar A, Revicki D, Treglia M, Buysse D. Measurement of non-restorative sleep in insomnia: A review of the literature. Sleep Medicine Reviews 2010;14(3):205-212.
[470] Veronese N, Koyanagi A, Solmi M, Thompson T, Maggi S, Schofield P, Mueller C, Gale CR, Cooper C, Stubbs B. Pain is not associated with cognitive decline in older adults: A four-year longitudinal study. Maturitas 2018;115:92-96.
[471] Vgontzas AN, Fernandez-Mendoza J, Liao D, Bixler EO. Insomnia with objective short sleep duration: the most biologically severe phenotype of the disorder. Sleep Med Rev 2013;17(4):241-254.
[472] Vincent K, Tracey I. Hormones and their Interaction with the Pain Experience. Rev Pain 2008;2(2):20-24.
[473] Vitton O, Gendreau M, Gendreau J, Kranzler J, Rao SG. A double-blind placebo-controlled trial of milnacipran in the treatment of fibromyalgia. Hum Psychopharmacol 2004;19 Suppl 1:S27-35.
[474] Vlaeyen JWS, Linton SJ. Fear-avoidance model of chronic musculoskeletal pain: 12 years on. PAIN 2012;153(6):1144-1147.
[475] Vogt BA, Berger GR, Derbyshire SW. Structural and functional dichotomy of human midcingulate cortex. Eur J Neurosci 2003;18(11):3134-3144.
[476] Walitt B, Čeko M, Khatiwada M, Gracely JL, Rayhan R, VanMeter JW, Gracely RH. Characterizing "fibrofog": Subjective appraisal, objective performance, and task-related brain activity during a working memory task. Neuroimage Clin 2016;11:173-180.
[477] Walitt B, Roebuck-Spencer T, Bleiberg J, Foster G, Weinstein A. Automated neuropsychiatric measurements of information processing in fibromyalgia. Rheumatology international 2008;28(6):561-566.
[478] Waller R, Smith AJ, O'Sullivan PB, Slater H, Sterling M, Straker LM. The association of early life stressors with pain sensitivity and pain experience at 22 years. Pain 2020;161(1):220-229.
[479] Walters SJ, Bonacho dos Anjos Henriques-Cadby I, Bortolami O, Flight L, Hind D, Jacques RM, Knox C, Nadin B, Rothwell J, Surtees M, Julious SA. Recruitment and retention of participants in randomised controlled trials: a review of trials funded and published by the United Kingdom Health Technology Assessment Programme. BMJ Open 2017;7(3):e015276.
[480] Wang J, Zuo X, He Y. Graph-based network analysis of resting-state functional MRI. Frontiers in systems neuroscience 2010;4:1419.
[481] Wanigasekera V, Lee MC, Rogers R, Kong Y, Leknes S, Andersson J, Tracey I. Baseline reward circuitry activity and trait reward responsiveness predict expression of opioid analgesia in healthy subjects. Proceedings of the National Academy of Sciences 2012;109(43):17705-17710.
[482] Warner NS, Hanson AC, Schulte PJ, Habermann EB, Warner DO, Mielke MM. Prescription opioids and longitudinal changes in cognitive function in older adults: A population-based observational study. J Am Geriatr Soc 2022;70(12):3526-3537.
[483] Warren SL, Heller W, Miller GA. The Structure of Executive Dysfunction in Depression and Anxiety. Journal of Affective Disorders 2021;279:208-216.
[484] Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, Buysse D, Dinges DF, Gangwisch J, Grandner MA, Kushida C, Malhotra RK, Martin JL, Patel SR, Quan SF, Tasali E. Recommended Amount of Sleep for a Healthy Adult: A Joint Consensus Statement of the American Academy of Sleep Medicine and Sleep Research Society. Sleep 2015;38(6):843-844.
[485] Wearing SC, Hennig EM, Byrne NM, Steele JR, Hills AP. The biomechanics of restricted movement in adult obesity. Obesity Reviews 2006;7(1):13-24.
[486] Weber F, Hoang Do JP, Chung S, Beier KT, Bikov M, Saffari Doost M, Dan Y. Regulation of REM and non-REM sleep by periaqueductal GABAergic neurons. Nature communications 2018;9(1):354.
[487] West SL, Savitz DA, Koch G, Strom BL, Guess HA, Hartzema A. Recall Accuracy for Prescription Medications: Self-report Compared with Database Information. American Journal of Epidemiology 1995;142(10):1103-1112.
[488] Whibley D, Stelfox K, Henry AL, Tang NK, Kratz AL. Development of a hybrid sleep and physical activity improvement intervention for adults with osteoarthritis-related pain and sleep disturbance: a focus group study with potential users. British Journal of Pain 2022;16(2):136-148.
[489] Whibley D, Williams D, Clauw D, Kratz A. The association between non-restorative sleep and diurnal patterns of cognitive function and fatigue in people with fibromyalgia and matched controls. Arthritis and Rheumatology 2019;71(Supplement 10):3984-3986.
[490] White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Statistics in Medicine 2011;30(4):377-399.
[491] Whitehead AL, Julious SA, Cooper CL, Campbell MJ. Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. Statistical Methods in Medical Research 2016;25(3):1057-1073.
[492] Whitlock EL, Diaz-Ramirez LG, Glymour MM, Boscardin WJ, Covinsky KE, Smith AK. Association Between Persistent Pain and Memory Decline and Dementia in a Longitudinal Cohort of Elders. JAMA Intern Med 2017;177(8):1146-1153.
[493] Wicherts JM. The importance of measurement invariance in neurocognitive ability testing. The Clinical Neuropsychologist 2016;30(7):1006-1016.
[494] Wichniak A, Wierzbicka A, Walęcka M, Jernajczyk W. Effects of Antidepressants on Sleep. Curr Psychiatry Rep 2017;19(9):63.

[495] Widaman KF, Ferrer E, Conger RD. Factorial Invariance Within Longitudinal Structural Equation Models: Measuring the Same Construct Across Time. Child Development Perspectives 2010;4(1):10-18.
[496] Wilckens KA, Woo SG, Kirk AR, Erickson KI, Wheeler ME. Role of sleep continuity and total sleep time in executive function across the adult lifespan. Psychology and aging 2014;29(3):658.
[497] Wilson SJ, Nutt DJ, Alford C, Argyropoulos SV, Baldwin DS, Bateson AN, Britton TC, Crowe C, Dijk DJ, Espie CA, Gringras P, Hajak G, Idzikowski C, Krystal AD, Nash JR, Selsick H, Sharpley AL, Wade AG. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. J Psychopharmacol 2010;24(11):1577-1601.
[498] Wolfe F, Cathey MA, Hawley DJ. A double-blind placebo controlled trial of fluoxetine in fibromyalgia. Scand J Rheumatol 1994;23(5):255-259.
[499] Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Hauser W, Katz RL, Mease PJ, Russell AS, Russell IJ, Walitt B. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum 2016;46(3):319-329.
[500] Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Häuser W, Katz RS, Mease P, Russell AS, Russell IJ, Winfield JB. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. J Rheumatol 2011;38(6):1113-1122.
[501] Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, Russell AS, Russell IJ, Winfield JB, Yunus MB. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis care & research 2010;62(5):600-610.
[502] Wolfe F, Walitt BT, Rasker JJ, Katz RS, Häuser W. The Use of Polysymptomatic Distress Categories in the Evaluation of Fibromyalgia (FM) and FM Severity. The Journal of Rheumatology 2015;42(8):1494-1501.
[503] Wong T-T. Performance evaluation of classification algorithms by k-fold and leave-one-out cross validation. Pattern Recognition 2015;48(9):2839-2846.
[504] Wood SN, Pya N, Säfken B. Smoothing parameter and model selection for general smooth models. Journal of the American Statistical Association 2016;111(516):1548-1563.
[505] Woolrich MW, Ripley BD, Brady M, Smith SM. Temporal autocorrelation in univariate linear modeling of FMRI data. Neuroimage 2001;14(6):1370-1386.
[506] Wu A, March L, Zheng X, Huang J, Wang X, Zhao J, Blyth FM, Smith E, Buchbinder R, Hoy D. Global low back pain prevalence and years lived with disability from 1990 to 2017: estimates from the Global Burden of Disease Study 2017. Annals of translational medicine 2020;8(6).
[507] Wu Y-L, Huang C-J, Fang S-C, Ko L-H, Tsai P-S. Cognitive Impairment in Fibromyalgia: A Meta-Analysis of Case-Control Studies. Psychosomatic medicine 2018;80(5):432-438.
[508] Xue J, Li H, Xu Z, Ma D, Guo R, Yang K, Wang Y. Paradoxical sleep deprivation aggravates and prolongs incision-induced pain hypersensitivity via BDNF signaling-mediated descending facilitation in rats. Neurochemical research 2018;43:2353-2361.
[509] Yang C-C, Keung Y-P, Wu C-H, Sun W-Z, Lin C-P. A preliminary investigation of dissociation between subjective cognitive complaints and objective cognitive impairments in female patients with fibromyalgia: a role of information processing speed. Clinical and experimental rheumatology 2024;42(6):1230-1239.
[510] Yang Q, Li S, Yang Y, Lin X, Yang M, Tian C, Mao J. Prolonged sleep duration as a predictor of cognitive decline: a meta-analysis encompassing 49 cohort studies. Neuroscience & Biobehavioral Reviews 2024:105817.
[511] Yang W, Han J, Luo J, Tang F, Fan L, Du Y, Yang L, Zhang J, Zhang H, Liu J. Connectome-based predictive modelling can predict follow-up craving after abstinence in individuals with opioid use disorders. Gen Psychiatr 2023;36(6):e101304.
[512] Yeephu S, Suthisisang C, Suttiruksa S, Prateepavanich P, Limampai P, Russell IJ. Efficacy and safety of mirtazapine in fibromyalgia syndrome patients: a randomized placebo-controlled pilot study. Ann Pharmacother 2013;47(7-8):921-932.
[513] Younger J, Noor N, McCue R, Mackey S. Low-dose naltrexone for the treatment of fibromyalgia: findings of a small, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial assessing daily pain levels. Arthritis Rheum 2013;65(2):529-538.
[514] Yuan H, Ahmed WL, Liu M, Tu S, Zhou F, Wang S. Contribution of pain to subsequent cognitive decline or dementia: A systematic review and meta-analysis of cohort studies. International journal of nursing studies 2023;138:104409.
[515] Yusuf S, Collins R, Peto R. Why do we need some large, simple randomized trials? Stat Med 1984;3(4):409-422.
[516] Zachariae R, Lyby MS, Ritterband LM, O'Toole MS. Efficacy of internet-delivered cognitive-behavioral therapy for insomnia - A systematic review and meta-analysis of randomized controlled trials. Sleep Med Rev 2016;30:1-10.
[517] Zainal NH, Newman MG. Executive function and other cognitive deficits are distal risk factors of generalized anxiety disorder 9 years later. Psychological Medicine 2018;48(12):2045-2053.
[518] Zambelli Z, Halstead EJ, Fidalgo AR, Mangar S, Dimitriou D. Telehealth delivery of adapted CBT-I for insomnia in chronic pain patients: a single arm feasibility study. Front Psychol 2023;14:1266368.
[519] Zhao S, Martin EM, Reuken PA, Scholcz A, Ganse-Dumrath A, Srowig A, Utech I, Kozik V, Radscheidt M, Brodoehl S. Long COVID is associated with severe cognitive slowing: a multicentre cross-sectional study. EClinicalMedicine 2024;68.
[520] Zhao S, Shibata K, Hellyer PJ, Trender W, Manohar S, Hampshire A, Husain M. Rapid vigilance and episodic memory decrements in COVID-19 survivors. Brain Communications 2022;4(1).
[521] Zhao S, Toniolo S, Hampshire A, Husain M. Effects of COVID-19 on cognition and brain health. Trends Cogn Sci 2023;27(11):1053-1067.
[522] Zhao W, Zhao L, Chang X, Lu X, Tu Y. Elevated dementia risk, cognitive decline, and hippocampal atrophy in multisite chronic pain. Proceedings of the National Academy of Sciences of the United States of America 2023;120(9):e2215192120.
[523] Zhuo M. Neural Mechanisms Underlying Anxiety–Chronic Pain Interactions. Trends in Neurosciences 2016;39(3):136-145.
[524] Zou Q, Ross TJ, Gu H, Geng X, Zuo XN, Hong LE, Gao JH, Stein EA, Zang YF, Yang Y. Intrinsic resting-state activity predicts working memory brain activation and behavioral performance. Hum Brain Mapp 2013;34(12):3204-3215.